(–)-Va in 3 ml absolute ether at –78°. The reaction mixture was stirred for 1.5 h. The excess sodium was decomposed with dry ammonium chloride and the reaction mixture allowed to warm up to room temperature (until complete removal of ammonia); the residue was then extracted with absolute ether. After stripping of the solvent the yellow oil was purified on a column (SiO_2, L40/100, benzene–acetone 1:1). Yield 42 mg (38%) (+)-VIIIa, R_f 0.48 (Silufol UV-254; benzene–acetone 1:1). IR spectrum: 1760 cm^{-1} (CO of β-lactam). PMR spectrum: 1.30 (3H, d, $CH_3C_{(3)}$); 2.90 (1H, m, 4-H; 3.08 (1H, m, 4-H); 3.42 (1H, M, 3-H). Mass spectrum: M^+ 85, M_{calc} 85; $[\alpha]_{300}^{20}$+54.1° (c 0.17, CCl_4). The analogous procedure gave from 1.3 mmoles (–)-Vb 43 mg (39%) (–)-VIIIb; the R_f value, IR and PMR spectra were identical to those of the compound (+)-VIIIa, $[\alpha]_{300}^{20}$-45.4° (c 0.15, CCl_4), however the course of the CD curve is antipodic (see Fig. 1).

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AZO COUPLING AND AMINOMETHYLATION OF 2,5-DIPHENYLPYRROLE AND ITS DERIVATIVES

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The azo coupling of 2,5-diphenylpyrrole with arenediazonium chlorides has given previously unknown 3-arylazopyrroles and 4-phenylazo-3-phenylhydrazono-3H-pyrrole. The methylation and reductive acetylation of the anylazo derivatives have led to N-methylarylazo and acetylamino derivatives of 2,5-diphenylpyrrole. 3-Amino-2,5-diphenylpyrrole has been obtained by the reduction of 3-p-chlorophenylazo-2,5-diphenylpyrrole. The aminomethylation of 2,5-diphenylpyrrole and its derivatives with bis(dialkylamino)methanes had led to aminomethyl derivatives.

Continuing investigations in the pyrrole series [1] with the aim of finding biologically active compounds, we have studied the azo coupling of 2,5-diphenylpyrrole with aryldiazonium chlorides. It has been established that, depending on the pH of the medium during azo coupling, either monoarylazo- (Ia, b) or 4-phenylazo-3-phenylhydrazono-2,5-diphenyl-3H-pyrroles (II) are formed. The methylation of compounds (Ia) and (II) takes place in each case at the nitrogen atom of the pyrrole ring with the formation of compounds (Ic) and (III), respectively.

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*Deceased.

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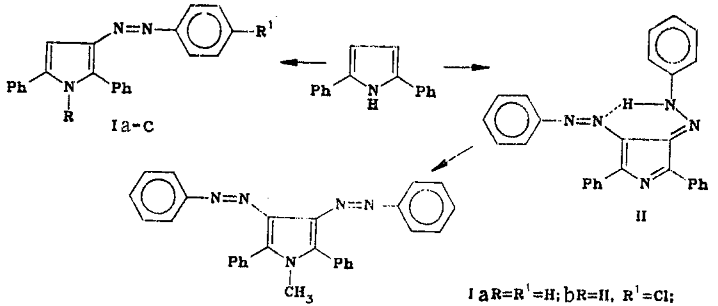


Ia-c

II

III

I a R=R^1=H; b R=H, R^1=Cl; c R=CH$_3$, R^1=Cl

The existence of compound (II) in the monophenylhydrazone form and not in the form of a diphenylazo derivative was confirmed by a comparative analysis of the IR, UV, PMR, and mass spectra of compounds (Ia), (II), and (III).

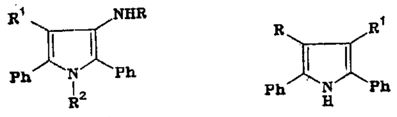
The IR spectrum of the arylazopyrrole (Ia) contains an absorption band of the NH group of a pyrrole at 3180 cm^{-1}, while in compound (II) this absorption band was detected neither in paraffin oil nor in a tablet with KBr nor in $CHCl_3$, while the absorption band at 3060 cm^{-1} observable in CCl_4 can be assigned either to the stretching vibrations of a NH group or to the stretching vibrations of the CH groups of an aromatic ring. It was impossible to confirm the structure of compound (I) unambiguously from its IR spectra.

In the PMR spectrum (DMSO-d_6) of compound (II), in addition to the multiplet of 20 aromatic protons in the 7.41-7.92 ppm region of a broadened signal was observed at 15.8 ppm of the proton of a NH group, which disappeared when deuteromethanol was added. The strong downfield shift or the signal of the NH proton is apparently connected with the formation of an intramolecular hydrogen bond, which is possible in the case of the anti-orientation of a substituent [2, 3].

As was to be expected [4, 5], in the UV spectra the long-wave absorption band at 480 nm in compound (II) was shifted hypsochromically by 125 nm in the spectrum of compound (III).

The mass spectra of compounds (Ia), (II), and (III) had strong peaks of the molecular ions (M^+ 323, 427, and 441, respectively*). In the case of compounds (Ia) and (III) under the action of electron impact, the objection of the phenylazo group from M^+ with the formation of fragments 218 (85)† and 336 (25), respectively, was observed. In the case of compound (III), the formation of a fragment $[PhCNCH_3]^+$, 118 (99), was also observed. The spectrum of compound (II) showed not only the elimination of a PhN_2 group from M^+ [ions at 322 (28)] but also the ejection of a PhNH group with the formation of a stable ion at 335 (100). Thus, a combination of the results of IR, UV, PMR, and mass spectroscopy confirms the structure of compound (II).

On the reductive acetylation of compounds (Ib, c) and (II) with zinc in acetic acid in the presence of acetic anhydride and sodium acetate at 50-60°C, the acetylaminoderivative (IVa-c) were obtained. The reduction of the arylazopyrrole (Ib) with sodium hydrosulfite, and also with zinc dust in a 1:1 mixture of ethanol and acetic acid led to 3-amino-2,5-diphenylpyrrole (IVd).



IVa-d Va-g

IV a—c R=$COCH_3$; d R=H; a, b, d R^1=H, c R^1=$NHCOCH_3$; a, c, d R^2=H, b R^2=CH_3; Va, f R=$CH_2N(CH_3)_2$, b R=CH_2-piperidino, c, e, g R=CH_2-morpholino, R=H; a, d R^1=$CH_2N(C_2H_5)_2$, b R^1=CH_2-piperidino, c R^1= CH_2-morpholino, e, f R^1= =N=N—C_6H_4Cl-*p*, g R^1=$NHCOCH_3$

We have shown that 3-arylazo- and 3-acetylamino-2,5-diphenylpyrroles take part in the aminomethylation reaction when they are heated with diaminomethanes in dioxane, while 2,5-

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*The numbers characterizing the ions show the m/z values.

†The intensities of the peaks in % with respect to the maximum peak are given in parentheses.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	T_{mp}*, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
Va	227—229	64,7	7,3	17,1	10,2	$C_{22}H_{27}N_3 \cdot 2HCl$	65	7,2	17,4	10,3	43
Vb	184—186	64,4	7,7	13,3	8,3	$C_{28}H_{35}N_3 \cdot 2HCl—2H_2O$	64,4	7,9	13,6	8,0	52
Vc	183—184	74,7	7,6	—	10,3	$C_{26}H_{31}N_3O_2$	74,8	7,5	—	10,1	60
Vd	190—192	73,8	7,4	10,5	8,1	$C_{21}H_{24}N_2 \cdot HCl$	73,9	7,4	10,4	8,1	40
Ve	200—202	71,2	5,6	7,7	12,7	$C_{27}H_{25}ClN_4O$	71,0	5,5	7,7	12,3	54
Vf	195—197	66,2	5,5	15,9	12,5	$C_{25}H_{23}ClN_4 \cdot HCl$	66,5	5,4	15,7	12,4	40
Vg	239—240	73,4	6,7	—	11,4	$C_{23}H_{25}N_3O_2$	73,6	6,7	—	11,2	62

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*Compounds (Va, b, f) were crystallized from methanol—acetone—ether, (Vc, g) from methanol, and (Ve) from methanol—DMFA (4:1).

diphenylpyrrole with a free position 3 is aminomethylated by these compounds only on heating in acetic acid. In this way the aminomethyl derivatives (Va-g) were obtained.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer instrument (Sweden) in paraffin oil, UV spectra on an EPS-3 spectrometer (Japan) in ethanol, and PMR spectra on a Varian XL-100 spectrometer with TMS as internal standard. Mass spectra were obtained on a Varian MAT-112 mass spectrometer (FRG) with a system for the introduction of the sample directly into the ion source at an energy of the ionizing electrons of 70 eV. The purity of the substances was checked by TLC on Silufol UV-254 plates in the benzene—ethyl acetate (4:1) and chloroform systems, the spots being revealed in UV light.

2,5-Diphenylpyrrole was obtained by the procedure of Overberger et al. [6].

2,5-Diphenyl-3-phenylazopyrrole (Ia). At from −5 to 0°C, with stirring a solution of benzenediazonium chloride prepared in the usual way from 1.4 g (15 mmoles) of aniline, 4.95 ml of concentrated hydrochloric acid, 16.5 ml of water, and 1.03 (15 mmoles) of sodium nitrite that had then been neutralized with sodium acetate of pH 6.0 was added gradually to a solution of 3.4 g (15 mmoles) of 2,5-diphenylpyrrole in 150 ml of methanol. The reaction mixture was stirred at 0°C for 0.5 h. The precipitate that had deposited was filtered off, washed with water, and dried. The yield of compound (Ia) was 2.23 g (45%), mp 149-149.5°C (benzene—hexane). IR spectrum, cm^{-1}: 3180 (NH), 1580, 1620 (C=C), 1400 (N=N). UV spectrum: λ_{max}, nm (log ε): 205 (4.58), 225 (4.30), 315 (4.77), 415 (4.24). PMR spectrum ($CDCl_3$), ppm: 7.38-7.94 (15 H, m, arom.); 7.0 (1 H, d, 4-H, $J_{1.4}$ = 3 Hz); 8.7 (1 H, s, NH). Mass spectrum, m/z (%): M^+ 323 (100): 322 (68); 246 (15); 218 (85). Found: C 81.7; H 5.5; N 13.0%. $C_{22}H_{17}N_3$. calculated: C 81.7; H 5.3; N 13.0%.

3-p-Chlorophenylazo-2,5-diphenylpyrrole (Ib). Compound (Ib) was obtained from 2,5-diphenylpyrrole and p-chloroaniline under the conditions for the synthesis of compound (Ia). Yield 94%, mp 196-197°C (from methanol—DMFA). IR spectrum, cm^{-1}: 3460 (NH), 1580, 1620 (C=C), 1400 (N=N). UV spectrum, λ_{max}, nm (log ε): 205 (4.32), 232 (4.18), 260 (4.18), 316 (4.55), 430 (4.16). Found: C 74.1; H 4.4; Cl 10.4; N 11.7%. $C_{22}H_{16}ClN_3$. Calculated: C 73.8; H 4.5; Cl 100; N 11.7%.

2,5-Diphenyl-4-phenylazo-3-phenylhydrazono-3H-pyrrole (II). At −5°C and pH 8-9 a solution of benzenediazonium chloride prepared in the usual way from 14.2 g (45 mmoles) of aniline, 10 ml of concentrated hydrochloric acid, and 3.1 g (45 mmoles) of sodium nitrite that had then been neutralized with sodium acetate to pH 3 was added gradually to a solution of 4.38 g (20 mmoles) of 2,5-diphenylpyrrole in 250 ml of methanol. The pH of the reaction mixture was kept constant by the simultaneous addition of a saturated solution of sodium carbonate. Then the reaction mixture was stirred at 0°C for 1 h. The precipitate was filtered off, washed with water, dried, and chromatographed on a column of KSK silica gel (benzene, chloroform). Yield 6 g (70%), mp 240-241°C (decomp., methanol—DMFA). IR spectrum, cm^{-1}: 3060 (NH). UV spectrum; λ_{max}, nm (log ε): 200 (4.12), 235 sh. (3.95), 295 (4.19), 480 (3.98). PMR spectrum (DMSO-d_6), ppm: 7.41-7.92 (20 H, m, arom.) 15.8 (1 H, br.s, NH). Mass spectrum, m/z (%): M^+ 427 (99); 426 (56); 350 (12); 335 (100); 322 (28); 105 (22); 92 (32); 77 (17). Found: C 78.4; H 5.1, N 16.7%. $C_{28}H_{21}N_5$. Calculated: C 78.4; H 5.0; N 16.4%.

3-p-Chlorophenylazo-1-methyl-2,5-diphenylpyrrole (Ic). At 10°C, a saturated solution of 2 g (50 mmoles) of caustic soda in water was added to a solution of 3.58 g (10 mmoles) of compound (Ib) in 50 ml of acetone. The reaction mixture was stirred for 5 min, and then 2.53 g (20 mmoles) of dimethyl sulfate was added dropwise. After further stirring for 20 min, the mixture was poured into water. The precipitate was filtered off, washed with water, and dried. Yield 2.65 g (71%); mp 172-174°C (from methanol—DMFA). UV spectrum, λ_{max}, nm (log ε): 206 (4.12), 250 (3.91), 300 (4.07), 390 (3.89). Found: C 74.2; H 5.1; Cl 9.8; N 11.3%. $C_{23}H_{18}ClN_3$. Calculated: C 74.3; H 4.9; Cl 9.5; N 11.3%.

1-Methyl-2,5-diphenyl-3,4-bisphenylazopyrrole (III). Compound (III) was obtained from (II) under the conditions of the synthesis of compound (Ic) with a yield of 97%; mp 200-201°C (from methanol). UV spectrum, λ_{max}, nm (log ε): 208 (4.54); 220 (shoulder) (4.33); 294 (4.46); 335 (4.27); PMR spectrum ($CDCl_3$), ppm: 3.54 (3 H, s, $H-CH_3$); 7.26-7.64 (18 H, m, arom.). Mass spectrum, m/z (%): M^+ 441 (100); 440 (18); 364 (65); 350 (4); 336 (25); 233 (23); 218 (10); 77 (30). Found: C 78.6; H 5.1; N 15.6%. $C_{29}H_{23}N_5$. Calculated: C 78.8; H 5.3; N 15.9%.

3-Acetylamino-2,5-diphenylpyrrole (IVa). With stirring, 9.18 g (90 mmoles) of acetic anhydride and 3.44 g (42 mmoles) of fused sodium acetate, and then, in portions, 11.7 g (180 mmoles) of zinc dust were added to a suspension of 10.7 g (30 mmoles) of compound (Ib) in 80 ml of glacial acetic acid, the temperature of the reaction mixture being maintained at 50-53°C. Then was stirred for 0.5 h, and the precipitate was filtered off and was washed with glacial acetic acid, and the mother solution was poured into water. The precipitate that deposited was filtered off, washed with water, and dried. The yield of compound (IVa) was 3.33 g (40%); mp 171-172°C (from aqueous methanol). IR spectrum, cm^{-1}: 3220, 3440 (NH), 1650 (C=O). UV spectrum, λ_{max}, nm (log ε): 205 (4.38), 232 (4.36), 325 (4.40). Mass spectrum, m/z (%): M^+ 276 (100), 234 (80); 233 (38), 206 (7), 130 (10), 127 (10), 105 (9), 103 (11), 77 (12), 44 (16), 43 (12). Found: C 78.2; H 5.8; N 10.1%. $C_{18}H_{16}N_2O$. Calculated: C 78.5; H 5.8; N 10.0%.

3-Acetylamino-1-methyl-2,5-diphenylpyrrole (IVb). In a similar manner to the preceding case, (IVb) was obtained from (Ic) with a yield of 62%; mp 78-79°C (from benzene—hexane). IR spectrum, cm^{-1}: 3230 (NH), 1650 (C=O). UV spectrum, λ_{max}, nm (log ε): 209 (4.32), 305 (4.22), Found: C 78.5; H 6.3; N 9.7%. $C_{19}H_{18}N_2O$. Calculated: C 78.6; H 6.2; N 9.6%.

3,4-Bisacetylamino-2,5-diphenylpyrrole (IVc). The compound (IVc) was obtained with a yield of 71% under the conditions for the synthesis of compound (IVa); mp 290-292°C (decomp., from methanol). IR spectrum, cm^{-1}: 3220 (NH), 1650 (C=O). UV spectrum, λ_{max}, nm (log ε): 208 (4.37), 220 sh. (4.18), 313 (4.36). Mass spectrum, m/z (%): M^+ 333 (100), 291 (67), 273 (80), 249 (32), 231 (22), 131 (30), 104 (27), 77 (21), 44 (39), 41 (48). Found: C 72.2; H 5.9; N 12.3%. $C_{20}H_{19}N_3O$. Calculated: C 72.0; H 5.7; N 12.6%.

3-Amino-2,5-diphenylpyrrole (IVd). A. To 65 ml of boiling water was added 8 g (40 mmoles) of sodium dithionite and then a boiling solution of 3.58 g (10 mmoles) of the arylazopyrrole (IIb) in 250 ml of ethanol. The reaction mixture was stirred for 1 h, filtered, and poured into water. The precipitate was filtered off, yield 2.08 g (89%), mp 186-187°C (benzene). According to the literature [7], mp 186-187°C.

B. A solution of 25.2 g (140 mmoles) of sodium dithionite in 90 ml of water was added to a solution of 10.8 g (30 mmoles) of compound (IIb) in 450 ml of glacial acetic acid at 70°C. The reaction mixture was stirred for 0.5 h and was then poured into water and neutralized with ammonia to pH 6. The precipitate was filtered off. Yield 6.2 g (88%), mp 186-187°C (benzene).

C. With stirring, 8.23 g (120 mmoles) of zinc dust was added to a suspension of 3.58 g (10 mmoles) of compound (IIb) in 300 ml of a 1:1 mixture of ethanol and acetic acid. The reaction mixture was stirred for 1 h, and then the precipitate was filtered off, and the filtrate was alkalinized with ammonia. The precipitate so formed was filtered off. Yield 1.87 g (80%), mp 186-187°C (benzene).

Preparation of Dialkylaminomethyl Derivatives of 2,5-Diphenylpyrrole (Va-g) (General Procedure). A mixture of 10 mmoles of 2,5-diphenylpyrrole, the arylazopyrrole (Ib), or the aminopyrrole (IVa) and 40 ml of dry dioxane* was boiled with 30 mmoles of a bis(dialkylamino)-methane derivative for 5 h. The solvent and the excess of amine were distilled off in vacuum. The residue was dissolved in absolute ether and was neutralized with an ethereal solution of hydrogen chloride. Information on compounds (Va-g) is given in Table 1.

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*The reaction of the 2,5-diphenylpyrrole was performed in acetic acid with heating in the water bath.

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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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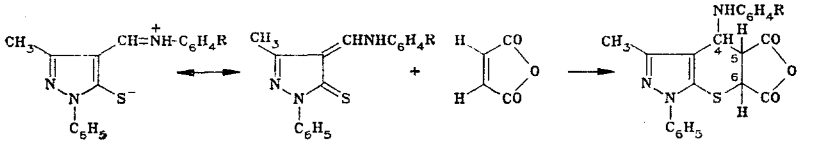
UDC 547.775:541.127

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:



I-XI

XII,XIII

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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