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REACTIONS OF 1-ARYL-2,5-DIMETHYLPYRROLES WITH KETONES

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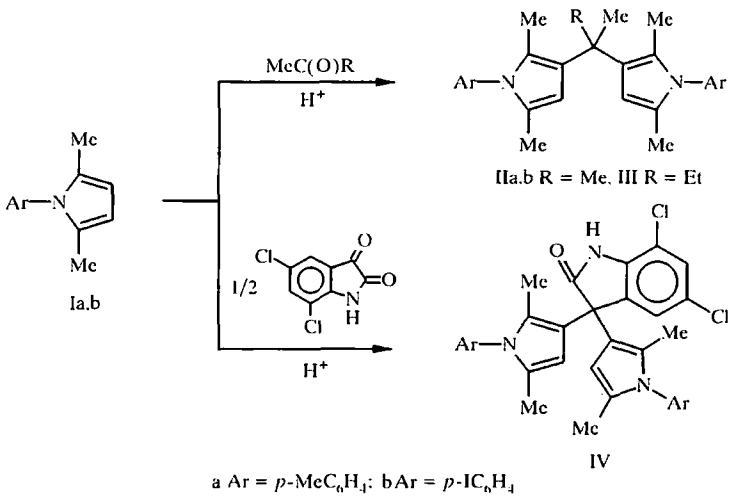
1-Aryl-2,5-dimethylpyrroles react with acyclic ketones with acid catalysis to give geminal di-2-pyrrolyl derivatives independently of the ratio of the reagents. The reaction of cyclohexanone and cycloheptanone occurs analogously with 2:1 ratio of pyrrole to ketone. With an excess of cyclohexanone or cycloheptanone 1-aryl-2,5-dimethyl-3,4-dicyclohexenylpyrroles and substituted 4,5,6,7,8,9-hexahydro-2H-azulene[1,2-c]pyrrol-4-spirocycloheptane are produced respectively.

Geminal dipyrrolyl derivatives or porphyrinogen cycles [1, 5, 7] are formed from the reaction of unsubstituted pyrroles and carbonyl compounds with acid catalysis. The same reactions are characteristic for 1H- and 1-alkyl-2,5-dimethylpyrroles [2-4, 6). The reaction of 1-aryl-2,5-dimethylpyrroles with carbonyl compounds has not been studied, apart from the reaction with 1,4-diketones, which gave N-arylisoindoles.

We have established that the direction of the reaction between 1-aryl-2,5-dimethylpyrroles and ketones depends on the structures of the ketone and the reagent ratio. Thus acyclic ketones and 5,7-dichloroisatin react with 1-aryl-2,5-dimethylpyrroles independently of the reagent ratio to give the geminal di-3-pyrrolyl derivatives II, III, and IV according to a known scheme [1-4].



a Ar = *p*-MeC_6H_4; b Ar = *p*-IC_6H_4

The reaction pathway of pyrroles I with cyclohexanone and cycloheptanone depends on the reaction conditions. With a pyrrole-ketone ratio of 2:1 the final products are the geminal di-3-pyrrolyl derivatives V and VI. The reaction of pyrroles I with an excess of cyclohexanone gave 1-aryl-3,4-dicyclohexenyl-2,5-dimethylpyrroles VII, while with an excess of cycloheptanone the spirocompound VIII was formed.

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Table 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	^{1}H NMR spectrum, δ, ppm	Yield, %
		C	H	N	I			
1	2	3	4	5	6	7	8	1
IIa*	$C_{29}H_{34}N_2$	84.68 / 84.87	8.22 / 8.29	6.86 / 6.82		158–159	1.59 (12H, br. s, CH_3); 2.0 (6H, s, CH_3); 2.93 (6H, s, CH_3); 5.97 (2H, s, CH); 7.0 (4H, d, CH); 7.2 (4H, d, CH)	98
IIb*[2]	$C_{29}H_{28}I_2N_2$				39.74 / 40.06	224–225	1.46 (6H, s, CH_3); 1.53 (6H, s, CH_3); 1.94 (6H, s, CH_3); 5.9 (2H, s, CH); 6.96 (4H, d, CH); 7.8 (4H, d, CH)	85
III*[2]	$C_{28}H_{30}I_2N_2$				38.83 / 39.19	160–161	0.78 (3H, t, CH_3); 1.39 (3H, s, CH_3); 1.51 (6H, s, CH_3); 1.87 (2H, q, CH2); 1.93 (6H, s, CH_3); 5.87 (2H, s, CH); 6.95 (4H, d, CH); 7.79 (4H, d, CH)	40
IV*	$C_{34}H_{31}Cl_2N_3O$	71.62 / 71.83	5.53 / 5.45	7.43 / 7.39		279	1.84 (6H, s, CH_3); 1.93 (6H, s, CH_3); 2.4 (6H, s, CH_3); 5.58 (2H, s, CH); 7.6 (4H, d, CH); 7.16 (1H, s, CH); ~7.22 (5H, d, CH^{*3}); 7.63 (1H, s, NH)	90
Va*	$C_{32}H_{38}N_2$	85.12 / 85.28	8.51 / 8.50	6.22 / 6.22		116–120	1.53 (2H, m, CH_2); 1.66 (10H, br. s. CH_3, CH_2); 2.01 (6H, s, CH_3)*; 2.13 (4H, m, CH_2); 2.4 (6H, s, CH_3); 6.02 (2H, s, CH); 7.03 (4H, d, CH); 7.2 (4H, d, CH)	90
Vb*	$C_{30}H_{32}I_2N_2$				37.17 / 37.63	216–218	1.51 (2H, m, CH_2); 1.62 (10H, br. s, CH_3, CH_2); 1.98 (6H, s, CH_3); 2.06 (4H, br. t, CH2); 6.01 (2H, s, CH); 6.85 (4H, d, CH); 7.72 (4H, d, CH)	45
VIa*	$C_{33}H_{40}N_2$	85.10 / 85.30	8.65 / 8.68	6.14 / 6.03		133–135	1.54 (6H, s, CH_3); 1.64 (4H, m, CH_2); 1.81 (4H, m, CH_2); 2.03 (6H, s, CH_3); 2.23 (4H, m, CH2); 2.41 (6H, s, CH_3); 6.0 (2H, s, CH); 7.0 (4H, d, CH); 7.23 (4H, d, CH)	83
VIb	$C_{31}H_{34}I_2N_2$				36.38 / 36.87	223	1.5 (3H, s, CH_3); 1.6 (4H, m, CH_2); 1.75 (4H, m, CH_2); 1.99 (6H, s, CH_3); 2.18 (4H, m, CH_2); 5.97 (2H, s, CH); 6.85 (4H, d, CH); 7.71 (4H, d, CH)	43

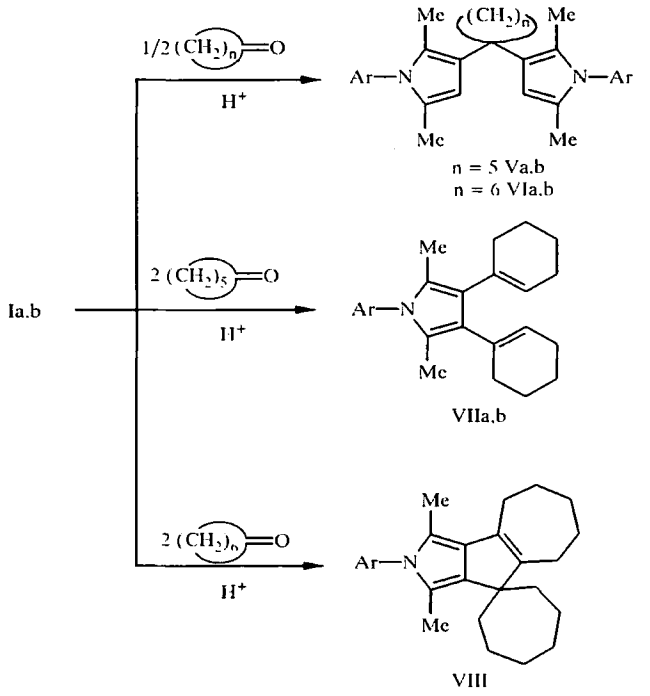
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
VIIa*[2]	$C_{23}H_{31}N$		M^+	$\frac{345}{345}$		139–140	1.61 (8H, m, CH_2); 1.88 (6H, s, CH_3); 2.1 (8H, m, CH_2); 2.38 (3H, s, CH_3); 5.45 (2H, br. s, CH); 7.15 (2H, d, CH); 7.3 (2H, d, CH)	93
VIIb*[2]	$C_{24}H_{28}IN$				$\frac{27.23}{27.75}$	101–102	1.6 (H, m, CH_2); 1.9 (6H, s, CH_3); 2.1 (8H, m, CH_2); 5.45 (2H, br. s, CH); 7.15 (2H, d, CH); 7.8 (2H, d, CH)	41
VIII*	$C_{27}H_{35}N$		M^+	$\frac{373}{373}$		133–135	1.66 (6H, m, CH_2); 1.7-1,8 (10H, m, CH_2 and CH_3*[3]); 1.91 (2H, m, CH_2); 2.08 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.38 (2H, m, CH_2); 2.41 (3H, s, CH_3); 2.58 (2H, m, CH_2); 7.1 (2H, d, CH); 7.25 (2H, d, CH)	58
IX*	$C_{31}H_{36}N_2$	$\frac{85.23}{85.27}$	$\frac{8.33}{8.31}$	$\frac{6.41}{6.42}$		107–109	1.56 (4H, m, CH_2); 1.8 (6H, s, CH_3); 2.1 (10H, br. s, CH_3, CH_2); 2.1 (6H, s, CH_3); 4.9 (4H, s, CH_2); 5.95 (2H, s, CH); 6.72 (4H, d, CH); 7.08 (6H, t, CH)	87

* $CDCl_3$.

*[2] DMSO-d_6.

*[3] Precise determination of chemical shifts is complicated by overlap of signals.



a Ar = *p*-MeC_6H_4–; b Ar = *p*-IC_6H_4–

The ^1H NMR spectra of compounds VIIa, b are characterized by a singlet at ~1.9 ppm corresponding to the methyl group of the pyrrole ring, a broad singlet at 5.45 ppm corresponding to an olefinic proton, and an absence of signals for the 3-H and 4-H protons of the pyrrole ring. The mass spectrum of compound VIIa contains a very intense molecular ion peak at *m/z* 345.

There is a complete absence of signals in the 3-7 ppm region of the ^1H NMR spectrum of compound VIII, but signals characteristic for the CH_3 and CH_2 groups occur in the 1.6-2.6 ppm region. In the ^{13}C NMR spectrum the signal of the spiro $C_{(4)}$ atom appears at 53.72 ppm (note the somewhat unusual shift for atom C Table 2 [9]). The mass spectrum contains a very intense molecular ion peak at *m/z* 373.

The formation of the various compounds when pyrroles I react with cyclohexanone and cycloheptanone is probably connected to the different sites of the nucleophilic attack by the second ketone molecule: in the case of the less bulky cyclohexanone it attacks the most electron rich $C_{(4)}$ atom of the pyrrole ring, whereas the more bulky cycloheptanone attacks the sp^2-hybridized atom of the cyclopentenyl ring. Formation of spiro compounds like VIII has also been noted in the reactions of ketones with other binucleophilic compounds, e.g., *o*-phenylenediamine [10].

The interaction of 1-aryl-2,5-dimethylpyrroles with cyclopentanone occurred unselectively to give a mixture of unidentified compounds, whereas 1-benzyl-2,5-dimethylpyrrole with cyclopentanone gave dipyrrolylcyclopentane IX in 90% yield under the same conditions.

The structures of compounds II-IX were confirmed by elemental analyses and ^1H NMR spectra, and ^{13}C NMR spectra for compounds Vb, VIb, VIIa, and VIII. The assignments of the signals are given in Tables 1 and 2.

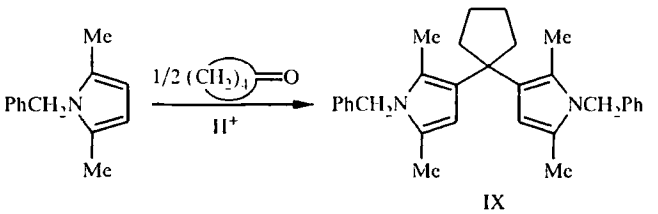


TABLE 2. ^{13}C NMR Spectra of Compounds Vb, VIb, VIIa, and VIII

Compound	Chemical shift, δ, ppm
Vb	12.22 (2-Me); 13.15 (5-Me); 23.3; 26.7; 38.46; 38.53 – signals of the cyclohexane ring carbon atoms; 92.32 (aryl-$C_{(4)}$); 107.66 ($C_{(4)}$); 124.03 ($C_{(3)}$); 125.56 and 127.44 ($C_{(2)}$ and $C_{(5)}$); 130.61 (aryl-$C_{(2)}$); 138.01 (aryl-$C_{(3)}$); 139.29 (aryl-$C_{(1)}$)
VIb	11.82 (2-Me); 13.08 (5-Me); 24.79; 31.32; 40.95; 41.37 – signals of the cycloheptane ring carbon atoms; 92.34 (aryl-$C_{(4)}$); 106.57 ($C_{(4)}$); 124.14 ($C_{(3)}$); 125.33 and 130.06 ($C_{(2)}$ and $C_{(5)}$); 130.5 (aryl-$C_{(2)}$); 138.03 (aryl-$C_{(3)}$); 139.29 (aryl-$C_{(1)}$)
VIIa	11.62 (2,5-Me); 21.07 (p-Me); 22.69; 23.61; 25.92; 30.13 – signals of the cyclohexene CH_2 groups 122.76 ($C_{(3)}$ and $C_{(4)}$); 123.86 ($C_{(2)}$ and $C_{(5)}$); 124.78 (cyclohex.-$C_{(2)}$); 128.12 (aryl-$C_{(2)}$); 129.44 (aryl-$C_{(3)}$); 133.8 (cyclohex. $C_{(1)}$); 136.8 (aryl-$C_{(1)}$); 136.9 (aryl-$C_{(4)}$)
VIII	11.32 (1-Me); 13.05 (3-Me); 21 (p-Me); 26.59; 31.89; 36.87 –signals of the spirocycloheptane CH_2 groups; 26.98; 27.27; 27.54; 27.9; 31.72 – signals of the cycloheptane CH_2 groups; 53.72 ($C_{(4)}$); 115.12 ($C_{(3a)}$); 119.57 ($C_{(9b)}$); 128.74 (aryl-$C_{(2)}$); 129.2 ($C_{(3)}$); 129.35 (aryl-$C_{(3)}$); 131.4 ($C_{(4a)}$); 134.7 ($C_{(1)}$); 136.75 (aryl-$C_{(1)}$); 136.78 (aryl-$C_{(4)}$); 153.8 ($C_{(9a)}$)

As a result of this work pyrroles which contain two nucleophilic centers separated by three (II-VI, IX) or four (VII) carbon atoms have been prepared. These compounds may be of interest for subsequent heterocyclization [11].

EXPERIMENTAL

^1H and group ^{13}C NMR spectra were recorded with a Varian VXR-300 spectrometer. ^{13}C NMR spectra were recorded under standard conditions with and without proton decoupling using the APT method. Solvents were $CDCl_3$ and DMSO-d_6 with TMS as internal standard. High resolution mass spectra were obtained with Hewlett Packard GC/MS-5890/5972A chromato-mass spectrometer. Purity and individuality of compounds were monitored by TLC (Silufol UV-254 strips with 5:1 nonane-butanol elution; spots revealed with iodine vapor or UV light). Elemental analysis results agreed with calculated values.

2,2-Di-(1-aryl-2,5-dimethylpyrrol-3-yl)propanes (II). One drop of conc. HCl was added to a solution of pyrrole I (2 g) in acetone (20 ml). The mixture was kept at 20°C for 1 h (until the solution became turbid). The solvent was evaporated at about 100°C and the residues was recrystallized from ethanol.

2,2-Di-[2,5-dimethyl-1-(*p*-iodophenyl)pyrrol-3-yl]butane (III) was synthesized analogously to compound II. Reaction time is 12 h.

3,3-Di-[2,5-dimethyl-1-(*p*-tolyl)pyrrol-3-yl]-5,7-dichloro-2-indolinone (IV). A solution of pyrrole Ia (5.4 mmol) and 5,7-dichloroisatin (2.7 mmol) in ethanol (20 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid was boiled for 3-4 h. The solution was cooled, the precipitate was filtered off and recrystallized from ethanol.

1,1-Di-(1-aryl-2,5-dimethylpyrrol-3-yl)cycloalkanes (V, VI). One drop of conc. HCl, followed by 2-3 more drops over the next hour, was added to a mixture of pyrrole I (5.4 mmol), a cyclic ketone (2.7 mmol), and ethanol (2 ml). The mixture was kept at 20°C until it solidified or thickened (5-24 h). It was then dissolved in propanol-2 on heating, cooled, and the precipitate removed and recrystallized from petroleum ether.

1-Aryl-3,4-di(cyclohexen-1-yl)-2,5-dimethylpyrroles (VII). Two drops of conc. HCl were added to a mixture of pyrrole I (5.4 mmol) and cyclohexanone (20 mmol) and the mixture was kept at 20°C until it thickened (16-24 h). The mixture was dissolved in propanol-2 and the precipitate was filtered off after 2-3 h and recrystallized from petroleum ether.

4,5,6,7,8,9-Hexahydro-1,3-dimethyl-2-*p*-tolyl-2H-azuleno[1,2-*c*]pyrrol-4-spirocycloheptane (VIII) was prepared analogously from pyrrole Ia (5.4 mmol) and cycloheptanone (20 mmol).

1,1-Di(1-benzyl-2,5-dimethylpyrrol-3-yl)cyclopentane (IX) was synthesized analogously to compounds V and VI.

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