

## ALKYLATION OF N-METHYLPYRROLE WITH *tert*-BUTANOL IN THE PRESENCE OF AMBERLYST 15 ION EXCHANGER

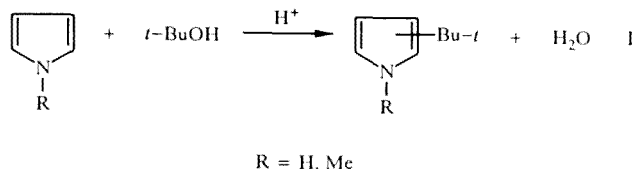
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*The 2- and 3-tert-butyl derivatives of 1-methylpyrrole, hitherto unknown, have been obtained by a single-stage method. The process is characterized by a low positional selectivity with a somewhat predominating  $\beta$ -substitution. The results have been compared with data, obtained by the quantum-chemical calculation of the molecules of pyrrole, N-methylpyrrole, and also of their  $\sigma$ -complexes with protons, introduced in the  $\alpha$ - and  $\beta$ -position of the rings.*

Continuing our investigations [1-5] of the electrophilic substitution in heterocyclic compounds, catalyzed by acidic ion-exchange resins in the present study we have investigated the reaction of N-methylpyrrole (I) with *tert*-butanol in the presence of the sulfocation exchanger Amberlyst 15 and proposed a simple single-stage method for the synthesis of hitherto unknown 2- and 3-*tert*-butyl-1-methylpyrroles (II and III).

*tert*-Butyl derivatives of pyrroles are usually obtained by Grignard reagents or by the Friedel-Crafts method with low yields, or by multistage syntheses from more complex derivatives [6-9]. In [2] 2- and 3-*tert*-butylpyrroles have been synthesized with a summary yield of 70% by refluxing (for 12 h) of a mixture of pyrrole (Pyr) with *tert*-butanol in the presence of Amberlyst 15 (molar ratio of reactants and catalyst 1:3:0.1).

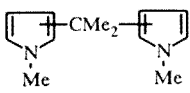
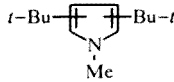
The results of the experiments which gave empirically the optimum conditions for the preparation of mono-*tert*-butyl derivatives of 1-methylpyrrole are presented in Table 1. Regardless of the strong basicity of the 1-methyl derivative in comparison with Pyr ( $pK_a$  Pyr -3.80,  $pK_a$  I -2.90 [10]; the same rule holds for the ionization potential: PI Pyr 8.21 V, PI I 8.09 eV [11]) it was found that the electrophilic reaction with the methyl-substituted pyrrole, given below, requires more severe conditions. Satisfactory yields of products II and III are obtained only by using significant excesses of *tert*-butanol and of the Amberlyst 15 cation exchanger (Table 1).



The main products of the reaction (R = Me) are two mono-*tert*-butyl derivatives of 1-methylpyrrole; two isomers of *i*-*tert*-butyl derivatives ( $M^+$  193) are also formed. At conditions, far from the optimum conditions, prolonged refluxing leads to three isomers of 2,2-bis(methylpyrrolyl)propane ( $M^+$  202), as determined by GC-mass spectrometry from the molecular ion peaks and the character of the ion decomposition. Vacuum distillation (73°C/14 mm Hg) isolated a mixture of two *tert*-butyl derivatives, a fraction enriched in the lowboiling isomer (ratio 1.8:1) to assist the interpretation of the  $^1\text{H}$  NMR spectra.

The  $^1\text{H}$  NMR spectra (Tables 2 and 3) identified the presence of  $\alpha$ - and  $\beta$ -isomeric *tert*-butyl derivatives of 1-methylpyrrole (II and III) in the mixture. The increments of the *tert*-butyl substituents (Table 2), obtained by comparing the chemical shifts of pyrrole [12] and  $\alpha$ - and  $\beta$ -*tert*-butylpyrroles [2] served as reference signals. The chemical shifts of II and

TABLE 1. Reaction of 1-Methylpyrrole with tert-Butanol in the Presence of Amberlyst 15 Resin

Exp. No.	Molar ratio I: tert-BuOH: Amb. 15*	Refluxing time, h	Conversion of I (GLC), %	Summary yield of II + III (GLC), %	Ratio of isomers <sup>*2</sup> II:III (GLC)	Side products <sup>*3</sup>
1	1 : 3 : 0,3	20	70	58	1 : 1,3	<p>Three isomers</p>  <p>(summary yield ~ 10%)</p>
2 <sup>*4</sup>	1 : 1 : 1	25	65	50	1 : 1,3	
3	1 : 10 : 1,5	15	78	63	1 : 1,3	<p>two isomers</p>  <p>(summary yield ~ 10%)</p>
4 <sup>*5</sup>	1 : 20 : 1,5	12	90	67	1 : 1,4	
5	1 : 30 : 2,5	8	98	82	1 : 1,4	

\*With account of the H<sup>+</sup> content, 4.6 meq/g.

\*<sup>2</sup>Identified by PMR spectra.

\*<sup>3</sup>Determined by GC-MS.

\*<sup>4</sup>In the inert solvent CCl<sub>4</sub>, concentration of I 20 vol. %.

\*<sup>5</sup>With stripping of the H<sub>2</sub>O-t-BuOH azeotropic mixture.

TABLE 2. Chemical Shifts in the <sup>1</sup>H NMR Spectra of Pyrroles ( $\delta$ , ppm against TMS, solvent CDCl<sub>3</sub>)

Protons	Pyr [12]	I [12]	2-tert-Butylpyrrole		3-tert-Butylpyrrole	
			[2]	increment*	[2]	increment*
H(1)			7,91		7,87	
H(5)	6,62	6,37	6,65	$z_{2,5}^{*2} + 0,03$	6,71	$z_{3,5} + 0,09$
H(2)	6,62	6,37	—	—	6,58	$z_{3,2} - 0,04$
H(4)	6,05	5,92	6,09	$z_{2,4} + 0,04$	6,16	$z_{3,4} + 0,13$
H(3)	6,05	5,92	5,92	$z_{2,3} - 0,13$	—	—
t-Bu			1,29		1,26	

\*Increment of tert-butyl substituent.

\*<sup>2</sup>In the increment  $z_{ij}$  the first subscript i indicates the position of the substituent and the second subscript j the position of the proton, the increment of which is cited.





III, calculated by adding increments to the shifts of the N-methylpyrrole proton [12], are very close to the experimentally measured shifts (Table 3). The presented experimental constants of spin-spin interaction (J, Hz) fit nicely into the intervals for pyrrole compounds, given in the literature [13]. It was found that the intensity of all signals, belonging to the  $\beta$ -isomer, is higher by approximately a factor of 1.8 than that of the  $\alpha$ -isomer, i.e., larger amounts of compound III than compound II are formed in the reaction.

The causes for the positional selectivity of the reactions of heterocyclic compounds with electrophiles are still not fully understood; for five-membered rings this characteristic decreases in the order furan > thiophene > pyrrole [11]. In the reaction studied by us this order is fully confirmed: furan is tert-butylied only in the  $\alpha$ -position, thiophene forms  $\alpha$ - and  $\beta$ -tert-butylthiophenes (ratio 3.5:1) while the ratio of  $\alpha$ - and  $\beta$ -tert-butylpyrroles is 1.7:1; in all these cases the  $\alpha$ -substitution

TABLE 3. Chemical Shifts and SSI Constants in the  $^1\text{H}$  NMR Spectra of 2- and tert-Butyl-1-methylpyrroles (II, III) ( $\sigma$ , ppm, reference TMS, solvent  $\text{CDCl}_3$ )

Protons	II		III		J (Hz)	
	Calc.	Experim.	Calc.	Experim.	[13]	Experim.
H(5)	6,40	6,47 (t)	6,46	6,48 (t)	$^4J_{2,4} = ^4J_{3,5} = 1,3\dots1,9$	1,8
H(2)	—	—	6,33	6,38 (t)	$^4J_{2,5} = 1,9\dots2,2$	2,0
H(4)	5,96	5,98 (t)	6,05	6,05 (t)	$^3J_{3,4} = 2,8\dots4,1$	3,6
H(3)	5,79	5,92 (qu)	—	—	$^3J_{4,5} = 2,3\dots3,2$	2,7
Me		3,71 (s)		3,57 (s)		
t-Bu		1,36 (s)		1,24 (s)		

TABLE 4. Quantum-Chemical Parameters of Pyrroles (calculated by the CONDO/2 method)

Characteristic	Atom	Pyrrole	N-Methylpyrrole
$\pi$ -Electron density at the atom, e	N	1,629	1,591
	C $\alpha$	1,093	1,101
	C $\beta$	1,091	1,084
Coefficient $p_z$ -AO in REMO	N	0,0	0,0
	C $\alpha$	0,595	0,595
	C $\beta$	0,382	0,380
Stabilization energy of the $\sigma$ -complex, kcal/mole		 323	 326
		 315	 320

predominates [1, 2]. A somewhat different result is obtained in the tert-butylation of 1-methylpyrrole. The positional selectivity in this instance is at a minimum (one of the isomers prevails only by 30-40%), whereby the  $\beta$ -isomer is the prevailing one.

In order to elucidate the causes of such a change in the direction of the reaction by the CONDO/2 method [14], we have carried out a quantum-chemical calculation of the pyrrole and 1-methylpyrrole molecules (Table 4). It is known [15] that the reactivity indices of different positions in the heterocycle are determined by the parameters of the corresponding atoms in the molecule; however, the values of some electron and energy characteristics of the C $\alpha$ - and C $\beta$ -atoms in the molecules of Pyr and I, and of the  $\sigma$ -complexes of the latter with a proton in these positions on the ring (Table 4) show that the introduction of a  $\text{CH}_3$  group in position 1 of the pyrrole ring does not lead to changes in the calculated values which would reveal the main route of the tert-butylation reaction of 1-methylpyrrole. The  $\pi$ -electron densities of the ring carbon atoms differ only little; the contributions to the frontal orbital which takes part in the reaction with the electrophiles (REMO) reflect more adequately the route of the reaction for pyrrole (the coefficient for C $\alpha$  is noticeably higher than for C $\beta$ ) and conform also with the stabilization energies of  $\sigma$ -complexes with protons. The latter characteristic explains also the decrease in the positional selectivity when a methyl group is introduced into the N-position: the difference in the stabilization energy is 8 for Pyr and 6 kcal/mole for I (Table 4). However, none of these parameters reveals the cause of the predominance of  $\beta$ -tert-butylation in the ring of compound I. In this instance the steric hindrances are probably of decisive importance, which are created for the alkylation reaction by the N— $\text{CH}_3$  group in the adjacent position to a larger degree than in the  $\beta$ -position. In the same way it was found [10] that particularly the steric effects are responsible for the ratios of the reaction products of  $\alpha$ - and  $\beta$ -electrophilic substitution (formylation, nitration) of N-substituted pyrroles. The introduction of a tert-butyl group as N-substituent (among the groups Et, Ph,  $\text{PhCH}_2$ ,  $\text{Me}_2\text{CH}$ , and t-Bu) most significantly changes the ratio in favor of  $\beta$ -substitution.

## EXPERIMENTAL

The  $^1\text{H}$  NMR spectra were recorded on Bruker WH-90/DS and Bruker WM-360 spectrometers (solvent  $\text{CDCl}_3$ , with TMS as internal standard). The GC-mass spectrometric analysis was carried out with Kratos MS-25 GC/MS (70 eV) equipment. The GLC analysis was performed on a Chrom-4 chromatograph with a flame ionization detector. A glass column (1.2 m  $\times$  3 mm) was packed with 10% SE-30 + 2.5% Reoplex-400 on Chromosorb W/AW, particle size 60-80 mesh. Nitrogen (60 ml/min) served as the carrier gas. The temperature of the column was 150°C, of the vaporizer 250°C. Amberlyst 15 cation exchanger ( $\text{H}^+$  form, exchange capacity 4.6 meq/g) and methylpyrrole were products of the firm Fluka, tert-butanol and  $\text{CCL}_4$  were analytical-grade.

The quantum-chemical calculations of the electron structure of the compounds were carried out by the semiempirical CONDO/2 method [14], by using the GEOMO program [16]. Complete optimization of the geometrical structure of the molecules and complexes was carried out in all cases. Experimental data in [17] were used as the initial structural parameters.

**2-tert-Butyl-1-methylpyrrole (II) and 3-tert-Butyl-1-methylpyrrole (III).** A mixture of 0.89 ml (10 mmole) 1-methylpyrrole, 28.7 ml (0.3 mole) tert-butanol, and 5.43 g (25 meq  $\text{H}^+$ ) of Amberlyst 15 resin is refluxed for 8 h with a reflux condenser and a  $\text{CaCl}_2$  tube with stirring on a magnetic stirrer to virtually complete conversion (control by GLC). The cation exchanger is filtered off and washed with carbon tetrachloride. The filtrate is dried over  $\text{CaCl}_2$ , evaporated on a rotary vacuum evaporator to a volume of  $\sim 5$  ml, and distilled in vacuum. The fraction 73-76°C/14-15 mm Hg (0.9 g) represents a mixture of II and III in the ratio 1:1.4 (GLC analysis, the first peak is the  $\beta$ -isomer, the second peak the  $\alpha$ -isomer); summary yield of II and III 65 mole % ( $^1\text{H}$  NMR spectra see Table 3). Mass spectrum (shown are the ion peaks with the relative intensity of more than 10%, m/z, II: 137 ( $\text{M}^+$ , 42), 122 (100), 107 (17), 94 (14), 82 (21); III: 137 ( $\text{M}^+$ , 38), 122 (100), 107 (11), 94 (14), 82 (23).

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