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ELECTROPHILIC ADDITION OF PHENOLS TO 1-VINYL-4,5,6,7-TETRAHYDROINDOLE

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Both uncatalyzed and acid-catalyzed (CH₃COOH) addition of phenols to 1-vinyl-4,5,6,7-tetrahydroindole gave 1-(1-aroxyethyl)-4,5,6,7-tetrahydroindoles. With increasing acidity of the phenol and in the presence of CF_3COOH the yield of adducts was lowered because of the oligomerization of 1-vinyl-4,5,6,7-tetrahydroindole.

The addition of phenols to 1-vinylpyrroles has received little attention, although this reaction gives a promising method of modifying the biological action of a series of complex phenol-like compounds by the introduction of a pyrrole ring. This reaction is also interesting because of the competition between the two nucleophilic centers — the α -position to the pyrrole nucleus and the vinyl group.

It is known that 1-vinylpyrroles [1, 2], in the presence of both protonic acids and Lewis acids (or combinations of the two) add alcohols to give the corresponding 1-(1-alkoxyethyl)pyrroles. With acids, 1-vinylpyrroles [3] form dimers and oligomers [4] — products of the electrophilic substitution of hydrogen in the pyrrole ring by an immonium cation, formed from another molecule.

In the present work, using 1-viny1-4,5,6,7-tetrahydroindole (I) as an example, the mechanism of the uncatalyzed and acid-catalyzed addition of phenols II-VI to 1-viny1pyrrole to give the previously unknown 1-(1-aroxyethy1)-4,5,6,7-tetrahydroindoles (VII-XI) has been studied (Table 1).



II, VII Ar=C₆H₅; III, VIII Ar=4-MeC₆H₄; IV, IX Ar=2-ClC₆H₄; V, X Ar=4-ClC₆H₄; VI, XI Ar=4-FC₆H₄

The discrepancy between the conversion of the starting pyrrole I (Table 1) and the yield of adduct was due to the fact that as well as addition of phenols to 1-vinyl group there also occurs the dimerization of the vinylpyrrole I to give 1-vinyl-2-[1-(1,4,5,6,7-tetrahydroindolyl)ethyl]-4,5,6,7-tetrahydroindole (XII) (from TLC data) [3].



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Com- pound	Empirical formula	bp,°C (Pa)	mp,°C	d₄²0	n _D ²⁰	Conver- sion of I,%	Yield of ad- duct, %
VII	C16H19NO	98116 [(6,76,4)×		1,0798	1,5540	79	60
VIII	C17H21NO	$ \times 10^{-2} $ 124130	31 34	1,0588	1,5534	74	57
IX	C ₁₆ H ₁₈ CINO	(0,1,1,0,-1) 124126 $[(3,63,9) \times$ $(3,63,9) \times$	4245	1,1435	1,5615	87	55
Х	C ₁₆ H ₁₈ ClNO	123125	57 61	1,1545	1,5665	~ 100	42
XI*	C ₁₆ H ₁₈ FNO	$134 \dots 136$ (1,3)		1,1084	1,5480	~ 100	23

TABLE 1. Conversion of Compound I and the Properties of 1-(1-Aroxyethyl)pyrroles VII-XI

*Reaction was carried out at 75°C for 20 h.

The initiator protons are generated in the medium by the dissociation of the phenol. The separation of the adducts VII-XI from the dimer XII is complicated by its ready solubility in these compounds and the similarity of its sublimation temperature to their boiling point; consequently as can be seen from IR spectral and TLC data, these adducts are contaminated with the dimer XII.

Oligomers of 1-viny1-4,5,6,7-tetrahydroindole were also isolated from the reaction mixture [4].

A more electron-attracting substituent in the phenol ring favors the conversion of the vinyl pyrrole I and at the same time the yield of the adduct decreases. This is because the more acidic the phenol, the greater the rate of dimerization and oligomerization of the pyrrole I; the concentration of the initiator protons increases, the nucleophilic character of the aryloxy-anions falls, and the probability of its reacting with the pyrrole ring is increased.

With a two-fold excess of phenol or in the presence of trifluoroacetic acid, a complete conversion of the pyrrole I is achieved, and the yield of adduct decreases (29 and 19% respectively).

According to [1], the addition of alcohols to 1-vinylpyrrole is reversible. However, the evidence for the reversibility of the reaction of addition of phenols to the pyrrole I could not be obtained. After keeping (6 h) the adduct VII in a sealed ampoule at 60°C, its characteristics (n_D^{20} , IR, PMR) did not change significantly, while the absorptions and signals corresponding to the impurities of phenol and pyrrole disappeared, i.e., in place of the expected increase in concentration of starting compounds a decrease occurred.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer, mass spectra on an MAT-212 (ionizing potential 70 eV). PMR spectra (10% solution in CDCl₃) were obtained on a Tesla BS-567A (100 MHz), internal standard HMDS.

Data for the synthesized compounds are given in Tables 1 and 2. Elemental analysis for C, H, N, and Hal agrees with calculated values.

<u>l-(l-Phenoxyethyl)-4,5,6,7-tetrahydroindole (VII)</u>. A. A mixture of 5.0 g (0.03 mmole) of pyrrole I and 3.2 g (0.03 mmole) of phenol was heated for 6 h at 60°C. Ether was added and the mixture washed with 30% KOH solution to remove the unreacted phenol. The ether solution was dried over K_2CO_3 , the ether driven off, and the residue fractionally distilled in vacuum. One gram (20% of the amount taken) of the pyrrole I was recovered and 3.9 g (60%) of the adduct VII was obtained as a clear, colorless liquid with a faint odor. Mass spectrum*: $[M]^+ 241, 147 - splitting off phenoxy radical.$

^{*}Value of m/z given.

	C-n pyr.ring						
Compound	CH pyr- role ring	0	C—N	pyrrole ring	pyrrole andbenz. ring	C—H	PMR spectra, ô, ppm
VII	690, 740, 790	1020, 1050, 1080	1330	1360, 1370, 1475	1580, 2980	2840, 2910	1,64 (4H,m, 5-H and 6-H); 1,75 (3H. d CH ₃); 2,43 (4H, m, 4-H and 7-H); 5.82 (1H, q, CH); 5,94 (1H, 3-H); 6,76 (1H, 2-H); 6,71, 6,79, 7,13 (5H, m, N-phenv1)
VIII*	700, 740	1030, 1060, 1090	1330	1350, 1360, 1470	1580, 2990	2850, 2930	1,68 (4H, m, 5-H and 6-H); 1,74 (3H, d, OCHCH ₃); 2,19 (3H, s, C ₆ H ₄ CH ₃); 2,41 (4H, m, 4-H and 7-H); 5,74 (1H, q, CH); 5,93 (1H, d, 3-H); 6,68 (1H, d, 2-H); 6,63 and 6,96 (4H, m, N-pheny1)
IX	680, 730	1010, 1030, 1060	1330	1350, 1360, 1460	1570, 2980	2830, 2910	1,63 (4H, m, 5-H and 6-H); 1,84 (3H, d, CH ₃); 2,42 (4H, m, 4-H and 7-H); 5,75 (1H, q, CH); 5,97 (1H, d, 3-H); 6,78 (1H, d, 2-H); 6,38 and 7,28 (4H, m, N-phenyl)
X	690, 710	1010, 1040, 1080	1330	1350, 1360, 1470	1570, 2980	2840, 2910	1,70 (4H, m, 5-Hand 6-H); 1,76 (1H, d, CH ₃); 2,41 (4H, m, 4-H and 7-H); 5,77 (1H, q, CH); 5,96 (1H, d, 3-H); 6,65 (1H, d, 2-H); 6,63 and 7,13 (4H, m, N-pheny1)
XI	690, 710	1050, 1070, 1090	1340	1370, 1385, 1500		1610, 2990	1,82 (3H, s CH ₃); 1,93 (4H, m, 5-H and 6-H); 2,57 (4H, m, 4-H and 7-H); 5,85 (1H, m, CH); 6,04 (1H, d., 3-H); 6,93 (1H, d, 2-H); 7,04 (4H, m, N-pheny1)

*Benzene ring 1500 cm⁻¹.

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B. The same reaction was carried out using a twofold excess of phenol and with the addition of CF_3COOH (0.2%) as catalyst; yield of adduct VII, 29 and 19% respectively.

<u>1-(1-Aroxyethyl)pyrroles VIII-XI</u> were obtained by method A, from the reaction between the pyrrole I and the phenols III-VI, taken in the molar ratio 1:1.

Examination of the reversibility of the addition reaction of phenols to pyrrole I. The adduct VII $(n_D^{-0} \ 1.5573)$ with a small amount of phenol as impurity (weak IR absorption at 3350 cm⁻¹, corresponding to the OH group) and the pyrrole I (IR absorption at 1620 cm⁻¹; PMR spectrum — two doublets at 4.4 and 4.7 ppm) was kept at 60°C in a sealed ampoule for 6 h. After this, the IR spectrum of the adduct $(n_D^{-0} \ 1.5540)$ showed no absorption at 3350 cm⁻¹ and the band at 1620 cm⁻¹ was smaller, while in the PMR spectra the signals at 4.4 and 4.7 ppm had disappeared.

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