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PYRROLES FROM KETOXIMES AND ACETYLENE

III.* CONJUGATION IN 2-ALKYL- AND 2, 3-DIALKYL-1-

VINYLPYRROLES AND THEIR ¹³C NMR SPECTRA

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The ¹³C NMR spectra of eight 2-alkyl- and 2,3-dialkyl-l-vinylpyrroles were studied. The ¹³C chemical shifts of all of the carbon atoms of the ring and the vinyl group depend substantially on the position and structure of the alkyl substituent. As the branched character of the alkyl group in the 2 position increases, the signal of the β -carbon atom of the vinyl group is shifted to weak field due to weakening of the p- π conjugation in the N-vinyl group because of disruption of its coplanarity with the pyrrole ring. The conjugation between the double bond and the pyrrole π system involves competition for possession of the p electrons of the nitrogen atom.

Detailed information regarding the electronic and conformation structures of pyrroles is necessary for a better understanding and prediction of their chemical behavior and physicochemical properties. However, up until recently the accumulation of this sort of information was deterred by the fact that it was difficult to obtain sufficiently representative series of substituted pyrroles. Systematic studies in this direction became possible after the discovery of the reaction of ketoximes with acetylene [2, 3], which makes it possible to easily obtain variously substituted pyrroles, including the previously unknown 1-vinylpyrroles.

The chemical shifts (CS) in the ¹³C NMR spectra can be used to estimate the total and π charge densities on the carbon atoms and particularly changes in these values [4, 5]. In the present research we studied the dependence of the ¹³C CS of 1-vinylpyrroles I-VIII on the position and structures of the alkyl substituents (R¹ and R²) in the hope of achieving a more thorough analysis of the nature of the mutual effect of the double bond and the pyrrole ring, the character of the p- π conjugation in the N-vinyl group, the transmission of the substituent effects through the pyrrole nitrogen atom, and the relative orientation of the π systems.



*See [16] for communication II.

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TABLE 1. ¹³C Chemical Shifts (in parts per million relative to tetramethylsilane) of 1-Vinylpyrroles I-VIII

Com- pound	R ¹	R²	C₂	C3	C₄	C₅	Cα	C _β
I* III IV V† VI† VII† VII†	$ \begin{array}{c} H \\ CH_3 \\ C_2H_5 \\ C_4H_9 \cdot t \\ C_2H_5 \\ C_4H_9 \cdot n \\ -(C \\ -(CH_2)_3C \end{array} $	H H H CH ₃ C ₃ H ₇ -n H ₂) ₄ — CH(CH ₃)—	118,18 127,66 134,12 140,44 130,73 128,50 127,21 131,60	110,14 108,38 106,92 106,59 115,26 121,34 118,86 117,96	110,14 109,34 109,62 108,41 111,72 110,37 109,65 109,33	118,18 115,46 115,88 118,25 114,45 114,69 114,46 114,94	132,83 130,33 130,55 133,41 130,22 130,86 130,41 130,40	95,89 96,55 97,01 98,48 95,50 95,39 94,75 94,71

*1³C chemical shifts of unsubstituted pyrrole [4]: 118.5, 108.2, 108.2, and 118.5 ppm (the order corresponds to the order in the table). +From [3].

This series of pyrroles, which includes 2-alkyl- and 2,3-dialkyl-l-vinylpyrroles with increasing branching of the substituent attached to C_2 , is primarily of interest for the establishment of the sensitivity of the ¹³C CS of the N-vinylpyrrole skeleton to the electronic and steric effects of the alkyl substituents.

It is apparent from Table 1 that substituents give rise to appreciable changes in the CS of the carbon atoms not only of the ring but also of the vinyl group. Since we are interested primarily in the character of the propagation of the effect of the substituents, we will examine the CS of the carbon atoms that are not directly attached to the alkyl group. The CS of the carbon atoms (C_5 and C_β) farthest away from the substituent unexpectedly display the highest sensitivity to alkyl substitution. The ranges of the changes in their CS reach 3.8 ppm, while the CS of the C_3 atom, which is closest to the R¹ substituent (for I-IV, which do not have a substituent attached to C_3), change over a range of 3.6 ppm, and the CS of C_4 and C_{α} (for the entire I-VIII series) range over 3.3 and 3.2 ppm. Such a long-range transmission of the effect and the selective sensitivities of the individual positions of the molecule are characteristic for π -electron mechanisms and confirm the presence of collectivized conjugation in N-vinylpyrroles.

Relative to unsubstituted pyrrole, the electron density on the C_3 and C_4 atoms in 1vinylpyrrole (I) is appreciably reduced (the CS increase by 3.88 ppm), as compared with a slight overall increase in the charge on C_2 and C_5 (the CS increase by a total of 0.64 ppm). One should expect precisely this sort of redistribution of the electron density in the case of competitive conjugation of the double bond with the p electrons of the nitrogen atom. According to [6, 7], the 160-200 ppm change in ¹³C CS corresponds to complete transfer of one π electron. In five-membered N-heterocycles the same redistributions of electron density correspond to even smaller changes in the ¹³C CS (according to the available estimates, 130 ppm per π electron [8] or 60 ppm per unit of overall charge density [9]). Consequently, the observed π electron perturbations (3-4 ppm) are estimated at 0.02-0.03 of the charge of the electron.

On passing to a more detailed analysis one must note the opposite character of the effect of the R¹ substituents on the CS of the carbon atoms of the ring and the β -carbon atom of the vinyl group. Let us examine the I-IV series. In complete conformity with the increase in the **donor-inductive** effect of R¹ (H < CH₃ < C₂H₅ < tert-C₄H₉) the C₃, C₄, and C₅ atoms are shielded monotonically (the C₅ atom when R¹ = tert-C₄H₉ constitutes an exception, which will be specially discussed). At the same time, the C_β atom is just as monotonically destined. This means that despite the reinforcement of the electron-donor effect of R¹ on passing from I to IV, the electron density of the double bond is shifted increasingly from the β position to the ring (as evidenced by the C_α CS), i.e., there is a progressive weakening of the PMR spectra of the same pyrroles [1] and also in series of alkyl vinyl ethers [10, 11], alkylvinyl sulfides [11], and alkoxy- and alkylthiobenzenes [12]. It has been demonstrated in all of these cases that the weakening of the p- π conjugation is due to the same effect – distortion of the coplanarity of the molecule when bulkier substituents are **present**.

The double bond of pyrrole II $(R^1 = CH_3)$ is less polarized than the double bond of pyrrole I (R¹ = H). The $C_{\alpha} - C_{\beta}$ difference, which characterizes the degree of polarization of the vinyl group, decreases in this case by 3.16 ppm (\sim 0.02 of the charge of the electron). It is apparent in the case of these compound that the deshielding of the β -carbon atom (0.66 ppm) is much less than the shielding of the α position (2.50 ppm). This means that a considerable portion of the electron density (1.84 ppm) enters into the double bond from the ring (the donor effect of the methyl group). This should primarily apply to the σ bonds (considering that R^1 is in the 2 position and also because of disruption of the coplanarity), as a consequency of which the long-range transmission of the charge is hindered.* The carbon skeleton of pyrrole II is actually deficient in electrons (the overall shielding is 4.20 ppm) as compared with pyrrole I. Since, of this value, only a portion of the electron density was transmitted to C_{α} , the residue (2.36 ppm) should increase the electron density on the nitrogen atom. This is in agreement with the increase in the relative basicities of Nvinylpyrroles when alkyl substituents are introduced in the ring [14]. In the light of these data one may more definitely solve the problem of the donor center of the pyrrole ring during the formation of an H bond with phenol that was advanced in [14]. From the CS of the ring carbon atoms it is apparent that the electron density in the 2 and 5 positions are not the maximum values (Table 1). They therefore cannot be the centers of primary attachment of the proton during the development of a weak H bond that does not substantially disrupt the electron distribution in the ring (during a study of the basicity from the Δv_{OH} shift of phenol [14]). As the number and donor strength of the alkyl substituents increase, the overall electron density on the ring carbon atoms decreases, and the basicity of the pyrrole as a whole, despite this, increases, and the donor center of the H bond is most likely the nitrogen atom.+

The C_5 and C_{α} nuclei in 2-ethyl-1-vinylpyrrole (III) are deshielded as compared with the corresponding methyl-substituted compound (II) by 0.42 and 0.22 ppm. On passing to tertbutyl homolog IV this deshielding increases abruptly, reaching 2.47 and 2.86 ppm, respectively This anomaly is also the result of conversion of the N-vinylpyrrole system to a nonplanar form because of steric interaction of the vinyl group with R¹. A steric interaction (through the corresponding protons) of C_{α} with R¹ and of C_{β} with C_5 exists in the planar anti form, and a steric interaction of C_{β} with R¹ exists in the syn form [1].



The observed CS of these nuclei should therefore be too low (as compared with compounds in which the indicated interaction is absent or weakened) by the value of the contribution of steric compression. On passing from $R^1 = C_2H_5$ to $R^1 = tert-C_4H_9$ realization of the planar forms (both syn and anti) is hindered markedly: The double bond deviates from the plane of the ring,[‡] thereby eliminating steric strain. As a result, the signals of the C₅ and C_{α} , nuclei are shifted sharply to weak field.

By comparison of the CS of 2-alkyl- and 2,3-dialkyl-l-vinylpyrroles (for example, III and V) one can arrive at the conclusion that the effect of the alkyl group attached to C₃ has the character of donor π induction: deshielding of the closest C₄ atom, and shielding of C₅ and C₆. It is noteworthy that C₆ "feels" the effect of the methyl group through five bonds,

*The effects of steric compression [13], which, however should not change the qualitative picture, were not taken into account in this reasoning.

+This does not contradict the fact that strong acids protonate the 2 and 5 positions, since in this case the direction of attack is determined by the stability of the resulting pyrrolinium cation.

‡ A stable gauche conformation develops or the population of the higher torsion levels relative to the C-N bond is increased substantially.

undergoing a 1.51 ppm shift of its signal to weak field, i.e., an even greater shift than in the case of C_5 , which is three bonds away from the substituent.



An additional shielding contribution to the CS of C_{β} due to rigid fixing of R¹ on the side away from the vinyl group is observed on passing to tetrahydroindoles VII and VIII; as a **consequence** of this, the vinyl group acquires additional possibilities for realization of coplanarity with the pyrrole ring.

Thus the results confirm the presence in N-vinyl pyrroles of a collectivized π system with an altered orientation of the planes of the double bond and the ring that easily transmits the weak effects along its entire length and alters its ability to conduct electronic effects as a function of the fraction of nonplanar conformations (or the degree of non-coplanarity).

EXPERIMENTAL

Pyrroles I-VIII were synthesized from the corresponding ketoximes and acetylene by the method in [2] (the preparative details are given in communication I of this series [1]). The ¹³C NMR spectra were obtained at 25.2 MHz with a Varian XL-100/12 spectrometer under frequency-scanning conditions (at 25°C). The samples were the pure liquids (since the N-vinylpyrroles, in contrast to N-unsubstituted pyrroles [15], are virtually nonassociated) containing 5% (by volume) tetramethylsilane as the internal standard for measurement of the ¹³C CS. An external standard (deuterium oxide) was used for stabilization of the resonance condition; it was placed in a capillary with a diameter of 1 mm, which was situated in an ampul with a diameter of 5 mm containing the investigated substance. An Ortec 546 accumulator, measuring 1024 channels, was used in some cases to improve the signal/noise ratio. For this purpose the ¹³C NMR spectra were recorded under ¹³C{¹H} heteronuclear double-resonance conditions with wide-field decoupling from the protons. The following double NMR methods were also used for the assignment of the closely located signals in the ¹³C spectra: partial decoupling (for the determina-tion of the number of protons attached to the individual ¹³C nuclei) and selective decoupling. The latter method, for example, made it possible to unambiguously assign the C3 and C4 atoms in the spectrum of II, in which these signals are less than 1 ppm apart from one another. Since the signals of the protons attached to C_3 , C_4 , and C_5 are represented in the PMR spectrum of this compound by a broad quartet, a triplet, and a quartet with narrow components and are not overlapped (the 'H CS are, respectively, 5.74, 5.99, and 6.70 ppm), selective irradiation of the signals of these protons with a strong radiofrequency field (monofrequency) makes it possible to see only an intense signal from the ¹³C nucleus directly bonded to it in the ¹³C NMR spectrum. Similar methods were also used in other cases. The accuracy in the measurement of the ¹³C CS was ± 0.02 ppm.

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AZAINDOLE DERIVATIVES

LIII.* NEW METHOD FOR THE SYNTHESIS OF

6-CHLORO-5-AZAINDOLINE

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1-Benzyl-6-hydroxy-7-cyano-5-azaindoline, which was converted to 6-chloro-5azaindoline through 6-hydroxy-5-azaindoline, was synthesized from 0-methylbutyrolactim through 1-benzyl-2-pyrrolidone, 1-benzyl-2-cyano(carbamoylmethylene)pyrrolidine, and the product of its condensation with dimethylformamide diethylacetal.

The reaction of dimethylformamide diethylacetal (I) with l-methyl-2-(cyanocarbamoylmethylene)pyrrolidine takes place at the amide NH₂ group to give the corresponding acylformamidine, which is readily cyclized to l-methyl-6-hydroxy-7-cyano-5-azaindoline [2]. In order to synthesize pyrroline-nitrogen-unsubstituted 5-azaindoline derivatives by a similar method we studied the condensation with I of 2-(cyanocarbamoylmethylene)pyrrolidine (II), obtained by reaction of 0-methylbutyrolactim (III) with cyanoacetamide.

However, the reaction of II with acetal I proceeded in a different way than the reaction with its N-methyl substituted derivative. Condensation took place at the amide nitrogen atom with closing of a pyrimidine ring through the NH group of the pyrrolidine ring and at the 3 position of the pyrrolidine fragment. The only reaction product, which was isolated in 74% yield, was 1-dimethylaminomethylene-7-oxo-8-cyano-1,2,3,7-tetrahydro-6-azaindolizine (IV).



*See [1] for communication LII.

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