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PYRROLES FROM KETOXIMES AND ACETYLENE

I.* STRUCTURAL SPECIFICITY OF THE REACTION WITH UNSYMMETRICAL KETOXIMES. PMR SPECTRA OF 1-VINYLPYRROLES AND THE EFFECTS OF ALKYL SUBSTITUENTS

B. A. Trofimov, A. I. Mikhaleva,
A. N. Vasil'ev, and M. V. Sigalov

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The reaction between ketoximes $CH_3(RCH_2)C=NOH$ and acetylene in the presence of KOH and dimethyl sulfoxide at 120°C leads exclusively to 1-vinyl-2-methyl-3-R-pyrroles in 73-87% yields. The regiospecificity of the reaction is disrupted when the temperature is raised, and the fraction of a second isomer (1-vinyl-2-RCH_2-pyrrole) reaches 20-50% at 140°C. Regioselectivity is not observed for $R^1CH_2(R^2CH_2)C=NOH$ (R^1 and R^2 = n-alkyl). The relative shifts of the signals of the ring protons and the vinyl group for a number of 2-alkyl-1-vinyl- and 2,3-dialkyl-1-vinylpyrroles were measured. Alkyl substituents have a distinct effect on the chemical shifts of the protons of the 4–5 bonds. As the volume of the 2-alkyl substituent increases the β protons of the N-vinyl group are deshielded by 0.10-0.13 ppm, and the 4-H ring proton is shielded by 0.05-0.16 ppm; this is explained by steric inhibition of the p–π conjugation in the N-vinyl group during an s-trans(anti)-gauche conformational transition.

The present communication is a continuation of a series of papers on the study of the reaction of ketoximes with acetylene, which leads to pyrroles and N-vinylpyrroles.

In the case of an unsymmetrical ketoxime this reaction in the presence of KOH and dimethyl sulfoxide (DMSO) gives [2] two isomeric pyrroles (or an N-vinylpyrrole in the case of excess acetylene).

The following questions are important for an understanding of the reaction mechanism and for better preparative use of the reaction: Which of the two groups of the ketoxime – the methyl or methylene group (when

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*This is actually communication XVI. The first publications (for example, see [1-3] and the literature cited in them) were not numbered.

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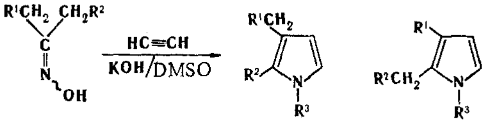


R^1=H, alkyl; R^2=alkyl; R^3=H, CH_2=CH

R^1=H) – primarily participates in the construction of the pyrrole ring? Are there differences in the reactivities of the two α-methylene groups (when R^1=alkyl and $R^1 \neq R^2$) related to different alkyl groups with normal structures? Do the reaction conditions affect the ratios of the structural isomers? The answers to these questions were obtained during a study of the reaction of a number of unsymmetrical ketoximes with acetylene under the influence of the KOH–DMSO system under conditions that lead to N-vinylpyrroles ($R^3 = CH_2{=}CH$). The ratios of the isomers were determined by gas–liquid chromatography (GLC) and PMR spectroscopy.

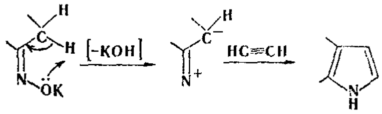
It follows from Table 1 that at 120°C all of the methyl alkyl ketoximes react with acetylene exclusively at the methylene group of the alkyl group, regardless of the structure (iso- or normal) of the remaining portion of the group, to give one isomer (pyrroles I, III, V, VII, and IX). The regiospecificity is disrupted as the temperature is raised: At 140°C pyrroles are formed through the methyl group (II, IV, VI, VIII, and X) in 20-50% amounts with respect to the mass of the mixture, i.e., in amounts completely acceptable for preparative separation, although the overall yields decrease.

Thus by selection of the conditions one can change the direction of the reaction and obtain not only 2,3-dialkyl-substituted products but also 3-unsubstituted pyrroles with different alkyl groups in the 2 position.

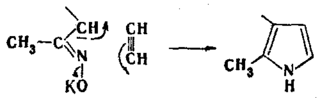
The two methylene groups of the two different alkyl groups with normal structures (for example, in the case of ethyl butyl ketoxime) have close reactivities: isomeric pyrroles IX and X are formed in approximately equal amounts even at 120°C.

The explanation for this should evidently be sought in the stereoisomerism of the starting ketoximes. It has been shown [4] that under the conditions of this reaction aldoximes do not form pyrroles but undergo 1,2-dehydration to give the corresponding nitriles in high yields.

One of the possible mechanisms of the pyrrole synthesis from ketoximes and acetylene includes 1,3-dehydration and subsequent addition of a 1,3 dipole to the triple bond:

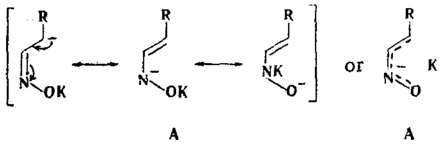


Strong bases readily detach the proton closest to the C=N bond (for example, in o-methyldibenzyl ketoxime [5], aldimines [6], and hydrazones [7]). Since the less sterically hindered and consequently more populated isomer of methyl alkyl ketoximes should have a syn-oriented methyl group with respect to the hydroxyl group, the "syn-1,3-dipoles" formed by splitting out of a proton from the methyl group lead to unstable azirines, whereas splitting out of a proton from the "anti-methylene" group gives a pyrrole:



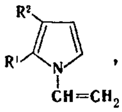
As the temperature is raised, the fraction of the isomeric ketoxime with a methyl group in the anti position relative to the hydroxyl group increases, and this leads to disruption of the structural specificity of the reaction.

Another factor that affects the structural specificity of the reaction may be the inductive effect of the groups.

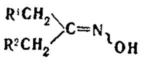


Carbanion A is more inclined to mesomeric stabilization, and its concentration in the reaction mixture is higher, the higher the donor capacity of R; i.e., in the case of competition between methyl and ethyl groups, a proton should primarily be provided by the latter.

TABLE 1. Yields and Ratios of the Regioisomers of 1-Vinylpyrroles



, Obtained from Unsymmetrical Ketoximes[a]



Ketoxime		1-Vinylpyrrole		Compound	120°[b]		140°[c]	
R¹	R²	R¹	R²		percentage in the mixture	overall yield, %	percentage in the mixture	overall yield, %
H	CH_3	CH_3 C_2H_5	CH_3 H	I II	99 1	73	65 35	33
H	n-C_3H_7	CH_3 n-C_4H_9	n-C_3H_7 H	III IV	100 0	83	79 21	61
H	i-C_3H_7	CH_3 i-C_4H_9	i-C_3H_7 H	V VI	100 0	87	50 50	36[d]
H	n-C_5H_{11}	CH_3 n-C_6H_{13}	n-C_5H_{11} H	VII VIII	100 0	76	70 30	35
CH_3	n-C_3H_7	C_2H_5 n-C_4H_9	n-C_3H_7 CH_3	IX X	50 50	75	50 50	50

[a] The ratios of the stereoisomers in the ketoximes were not determined. [b] Reaction conditions: 3 h, 30% KOH based on the weight of the ketoxime, ketoxime : DMSO ratio 1 : 10, initial acetylene pressure 10-14 gage atm. [c] Reaction conditions: 10% KOH based on the weight of the ketoxime, ketoxime : DMSO ratio 1 : 4, and the remaining conditions as in footnote b. [d] Ketoxime : DMSO ratio 1 : 8.

TABLE 2. Physicochemical Characteristics of the 1-Vinylpyrroles[a]

Compound[b]	bp, °C (mm)	d_4^{20}	n_D^{20}	Found, %			Empirical formula	Calc., %		
				C	H	N		C	H	N
I	71 (20)	0,9297	1,5270	79.2	9.1	11,7	$C_6H_{11}N$	79,3	9,2	11,6
III	63 (2)	0,9141	1,5159	80,4	10.0	9,3	$C_{10}H_{15}N$	80,5	10,1	9,4
V	74 (10)	0,9016	1,5150	80,6	10,3	9,1	$C_{10}H_{15}N$	80,5	10,1	9,4
VII	86 (2)	0.8753	1,5078	81,8	10,5	7,8	$C_{12}H_{19}N$	81,4	10,7	7,9
IX	74 (3)	0,8913	1,5082	81,3	10.5	8,4	$C_{11}H_{17}N$	80,9	10,5	8,6

[a] Pyrroles II, IV, VI, and VIII were not isolated from the mixtures with the corresponding structural isomers. [b] The numbering corresponds to that in Table 1.

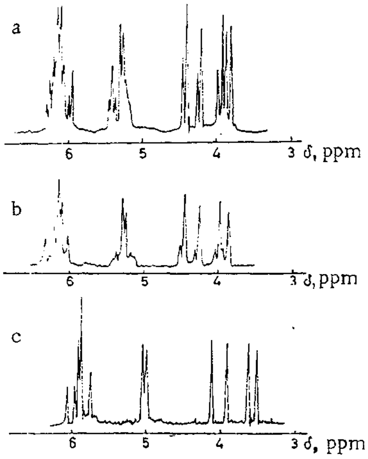
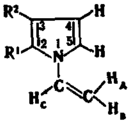


Fig. 1. PMR spectra: a) 1-vinyl-2,3-dimethylpyrrole (I) and 1-vinyl-2-ethylpyrrole (II), 65 : 35%, respectively; b) 1-vinyl-2-methyl-3-n-propylpyrrole (III) and 1-vinyl-2-n-butylpyrrole (IV), 80 : 20%, respectively; c) pure pyrrole (III).

TABLE 3. Chemical Shifts[a] of the Protons (δ, ppm) of 1-Vinylpyrroles



Compound	R¹	R²	A—H	B—H	C—H	4-H	5-H	R¹	R²
I	CH_3	CH_3	4,84	4,39	6,71	5,80	6,70	2,03,	1,90
II	C_2H_5	H	4,90	4,46	6,73	5,75	6,7	2,35(α)[b], 1,10(β)	5,96
III	CH_3	n-C_3H_7	4,89	4,42	6,72	5,85	6,70	2,05	2,27(α), 1,74(β), 1,10(γ)
IV	n-C_4H_9	H	4,94	4,48	6,72	5,73	6,7	2,40(α), 1,49(β,γ), 0,90(δ)	5,92
V	CH_3	i C_3H_7	4,87	4,42	6,73	5,90	6,70	2,10	2,75(α), 1,10(β)
VI	i-C_4H_9	H	4,94	4,52	6,74	5,74	6,7	2,43(α), 1,70(β), 0,90(γ)	5,93
VII	CH_3	n-C_5H_{11}	4,87	4,42	6,72	5,87	6,70	2,07	2,30(α), 1,32(β,γ,δ), 0,90(ε)
VIII	n-C_6H_{13}	H	4,94	4,49	6,73	5,72	6,7	2,52(α), 1,32(β,γ,δ,ε), 0,88(ω)	5,95
X	n-C_4H_9	CH_3	4,87	4,44	6,73	5,65	6,88	2,27(α), 1,31(β,γ), 0,90(δ)	1,98
IX	C_2H_5	n-C_3H_7	4,86	4,45	6,74	5,67	6,89	2,52(α), 1,06(β)	2,48(α), 1,20(β), 0,90(γ)

[a] The following SSCC were observed in the spectra of all of the compounds: $^2J_{AB} \cong 0.8$ Hz, $^3J_{AC} \cong 16.0$ Hz, $^3J_{BC} \cong 9.0$ Hz, and $^3J_{45} \cong 2.5$ Hz. [b] These are the protons attached to the α, β, etc. carbon atoms in R¹ and R² starting from the ring.

The PMR spectra of 2,3-dialkyl-1-vinylpyrroles have been described in one of our first communications [2] in this series. These studies have been continued in the present research in order to evaluate the sensitivity of the 1-vinylpyrrole π system to the effect of alkyl substituents in the 2 and 3 positions.

The J_{HH} spin–spin coupling constants (SSCC) in this series change only slightly [2]. We therefore thoroughly analyzed only the chemical shifts of the protons of the vinyl group (A–C) and the pyrrole ring (in the 4 and 5 positions). Although the chemical shifts of these protons also depend only slightly on the structures of the alkyl groups in the 2 and 3 positions, changing only by a few hundredths of parts per million [2], there is a possibility of unambiguous estimation of their relative shifts by recording the spectra of mixed samples. The spectra of two paired mixtures (I and II and III and IV) and one pure pyrrole (III) are reproduced in Fig. 1. It is quite apparent that there is no doubt about the assignment and direction of the shifts of the signals of the indicator protons. By means of this comparison of the spectra of pure pyrroles and mixtures of them one can confidently measure extremely small shifts in the signals. Since only the spectra of structural isomers (I and II, III and IV, etc.), one of which has an alkyl group in the 2 position, the other of which has alkyl groups in the 2 and 3 positions, were recorded in the paired combinations, the difference in the chemical shifts only between these pairs should be regarded as absolutely significant. In addition, because of superimposition of the corresponding multiplets, the accuracy in the measurements of the chemical shifts of the C–H and 5-H signals is lower than in the case of A–H, B–H, and 4-H.

The first thing that strikes one upon comparison of the data in Table 3 is the systematically lower shielding of the A–H and B–H vinyl protons and the systematically higher shielding of the 4-H protons in 2-alkylpyrroles II, IV, VI, and VIII as compared with 2,3-dialkyl-substituted I, III, V, and VII. A second striking feature is the distinct sensitivity of the position of the signals of these protons to a change in the structures of R¹ and R², which are located four and five bonds away from them, vis-a-vis the constancy of the chemical shifts of the closer C–H and 5-H protons. If the reason for this is the σ- or π-donor effect of the alkyl groups, this might have explained the greater shielding of the β protons of the vinyl group in the odd members of the series (0.05–0.07 ppm for A–H and 0.07–0.10 ppm for B–H), but the deshielding of their 4-H protons (0.05–0.16 ppm) is not in agreement with this. A paradoxical pattern is observed: Donor substituents lower the electron density in the heteroaromatic ring and increase it on the farthest removed atoms of the vinyl group. Such long-range effects are undoubtedly due to interaction of the π-electron systems of the molecule through the nitrogen heteroatom. If $p-\pi$ conjugation of the type

$$[\rangle\ddot{N}-CH=CH_2 \longleftrightarrow \rangle\overset{+}{N}=CH-\overset{-}{C}H_2]$$

is realized in the N-vinyl group [as evidenced by the considerable strong-field shifts of the signals of the β protons [2] and β carbon [2] (in the ^{13}C NMR spectrum) of the vinyl group as compared with ethylene], this effect should lead to a certain degree of "transfer" of electrons from the pyrrole ring, i.e., to deshielding of the 4-H proton. The intensity of $p-\pi$ conjugation decreases when the vinyl group deviates from the plane of the ring. The A–H and B–H chemical shifts therefore increase and the 4-H chemical shifts therefore decrease on passing from 2-methyl-substituted I, III, V, and VII to pyrroles of the even series with bulkier substituents in the 2 position. The isomeric IX and X pair, on the other hand, display very slight changes in the chemical shifts of all of the indicator protons; this is associated with the closeness of the effective volumes of the groups in the 2 position. Thus steric inhibition of $p-\pi$ conjugation in the N-vinyl group is displayed by adjacent alkyl substituents. Similar effects have been observed in the case of vinyl ethers and sulfides [8] and alkoxy- [9] and alkylthiobenzenes [10].

The results of this research confirm the assumption of the existence of a nonplanar conformation of N-vinylpyrroles that was made during a study of their relative basicities [11] and UV [12] and IR [13] spectra. The chemical shifts of the β proton syn-oriented with respect to the heteroatom undergo the greatest changes in the spectra of alkyl vinyl ethers and sulfides [8] when the volume of the alkyl group is varied; this is in agreement with a cis(syn)–gauche conformational transition. In the spectra of vinylpyrroles I-X the chemical shifts of both β-vinyl protons change over the same range (the range of change in the chemical shifts of the H–B vinyl proton anti-oriented relative to the $C_{sp^2}-N$ bond even somewhat exceeds the range for A–H: 0.13 and 0.10 ppm, respectively). This confirms the previous conclusion [2] that of the two possible planar conformations of 2-substituted N-vinylpyrroles, the "preferred" conformation is the anti(trans) form, in which the distance of the β-vinyl protons from substituent R^1 is a maximum.

EXPERIMENTAL

Analysis by GLC was carried out with a Khrom-4 chromatograph; the detector was a catharometer, the column was 2.5-m long and had a diameter of 3 mm, the solid phase was Chromaton N-AW-DMCS, the liquid phase was 15% DS-550 silicone, the thermostat temperature was 170°C, and helium was the carrier gas. The PMR spectra of 10% solutions of the compounds were recorded with a BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard (in the case of CCl_4 solutions).

Reaction of Methyl Ethyl Ketoxime with Acetylene. A) A mixture of 10 g (0.11 mole) of methyl ethyl ketoxime, 3 g of KOH, and 100 ml of DMSO was heated at 120°C for 3 h with acetylene (initial pressure 12 atm; a total of 21 liters was fed into the mixture) in a 1-liter rotating autoclave, after which the mixture was washed with water, and the organic layer was combined with the ether extracts obtained by extraction of the aqueous layer and dried with potassium carbonate. Vacuum distillation gave 9.7 g of 1-vinyl-2,3-dimethylpyrrole containing ~1% 1-vinyl-2-ethylpyrrole (Tables 1 and 2).

B) Similarly, 4.2 g of a mixture consisting of 35% 1-vinyl-2-ethylpyrrole and 65% 1-vinyl-2,3-dimethylpyrrole (Table 1) was obtained from 10 g (0.11 mole) of methyl ethyl ketoxime and 1 g of KOH in 40 ml of DMSO by reaction with 21 liters of acetylene at 140°C.

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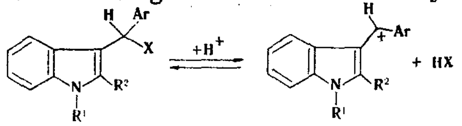
STRUCTURE OF INDOLYLPHENYLMETHYL CATIONS

N. A. Kogan and G. N. Kul'bitskii

UDC 547.759.1:543.422.25

The charge distribution in 1-methyl-2-carboxy-3-indolylphenylmethyl cation (II), which is formed by dissociation of the C−X bond in 1-methyl-2-carboxy-3-(α-X-benzyl)indoles (I) in H_2SO_4 solution, was studied by PMR and ^{13}C NMR spectroscopy. Cation II may have a structure with a positive charge on the benzyl carbon atom (IIa), the nitrogen atom (IIc), or on the α-carbon atom of the indole ring (IIc). Structures IIc and IIa make the major contributions to the II structure; this is confirmed by calculations by the Pariser−Parr−Pople (PPP) method within the σ−π approximation.

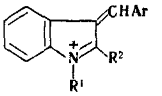
The behavior of various indoles in strongly acidic media has demonstrated that alkyl-substituted indoles are protonated in the 3 position to give an indolenine structure with localization of the positive charge on the nitrogen atom [1]. The high probability of a structure with the cationic center in the 2 position of indole has been established by calculations [2]. We have previously investigated the behavior in sulfuric acid solution of 3-(α-chlorobenzyl)indoles, which, in contrast to other alkyl-substituted indoles, form cations through dissociation of the carbon−chlorine bond via the following scheme rather than by the addition of a proton [3]:



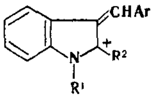
I IIa

X = OH, Cl; $R^1 = CH_3$; $R^2 = COOH$; $Ar = C_6H_5$; $o\text{-}C_6H_4Cl$; o-, m-, $p\text{-}C_6H_4NO_2$

The existence of two other resonance structures with the charge on the nitrogen atom (IIb) − the indolium cation [4] − and with the charge in the 2 position (IIc) is possible for the 3-indolylphenylmethyl cation (IIa):



IIb



IIc

In view of their insignificant contributions, we will not examine structures with the charge in the benzene ring of indole, which lead to doubly charged ions, and structures with the charge in the benzene ring in the side chain, which lead to quinoid structures.

To estimate the contributions of IIa,b,c to the structure of ionized chlorides I, we used the data from the PMR and ^{13}C NMR spectra and the results of calculations of the charge distribution and bond orders by the Pariser−Parr−Pople (PPP) method within the Dewar π−σ approximation [5] for the IIa cation, where $R^1 = H$, $R^2 = COOH$, and $Ar = o\text{-}ClC_6H_4$.

A multiplet of aromatic protons and a singlet of the NCH_3 group are observed in the PMR spectrum (Fig. 1) of I in D_2SO_4; the signal of the carboxyl proton is not observed because of rapid exchange. The 1H singlet

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