

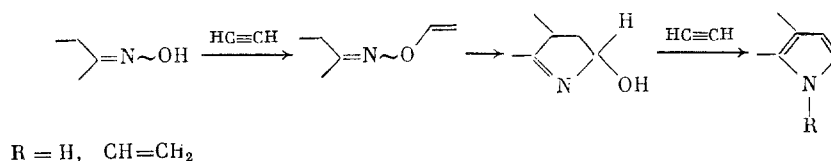
CYCLOALKA[b]PYRROLES FROM KETOXIMES AND ACETYLENE:
SYNTHESIS AND KINETIC INVESTIGATION

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The rate constants of formation of cycloalka[b]pyrroles and their N-vinyl derivatives were determined, and it was shown that efficient preparation of pyrroles condensed with aliphatic macrocycles from the corresponding ketoximes and acetylene in the KOH-DMSO system is possible.

The reaction of ketoximes with acetylenes in the superbasic KOH-DMSO system, affording pyrroles and N-vinylpyrroles, occurs according to the scheme [1]



Despite the efficiency and universality of this reaction [1], unsuccessful attempts at the pyrrolization of cyclopentanone [1] and cyclooctanone oximes [2] are known, which led us to carry out an additional investigation.

The purpose of the present paper is a study of the kinetics of the reaction of cycloalkanone oximes with acetylene and the effect of the ring size on its rate. Figure 1 shows a family of typical kinetic curves obtained as a result of GLC analysis of the reaction mixture using cyclohexanone oxime. The limiting reaction step is the reaction of acetylene with potassium oximate, which is actually a precursor of pyrrole, because the chain of intermediate conversions, which is characteristic, for example, of the formation of pyrroles with a phenyl substituent [1], occurs much faster. In Fig. 1, curve b has an S-shaped nature

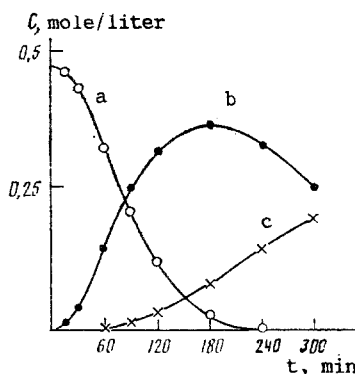


Fig. 1. Relation of concentrations of cyclohexanone oxime (a), 4,5,6,7-tetrahydroindole (b), and N-vinyl-4,5,6,7-tetrahydroindole (c) to time at 86°C and acetylene pressure 720 ± 10 torr.

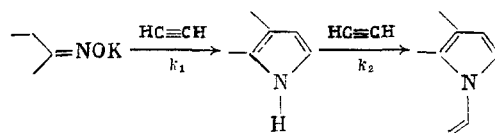
TABLE 1. Effective Rate Constants of Pseudo-First-Order Reaction* (k , sec^{-1} , T 86°C , PC_2H_2 720 ± 10 mm Hg)

Ring size in oxime	$k_1 \cdot 10^5$	$k_2 \cdot 10^5$
C_5	Pyrroles not detected	
C_6	25 (81 [1])	1.9 (93 [1])
2-Me- C_6	23 (70 [1])	1.8 (80 [1])
4-Me- C_6	26	1.9
C_7	2.9 (79 [1])	1.3
C_8	17 (60)	1.5 (~100)
C_{12}	2.1	1.1 (~100)

*The yields of the recovered compounds, %, are in parentheses.

in the initial region, which, most probably, is due to the rate of potassium oximate formation, which is comparable to the rate of pyrrole formation. The potassium oximate formation process occurs differently in the presence of acetylene and without it. It was determined that potassium cyclohexanone oximate, which is sparingly soluble in DMSO at 20°C ($<5 \cdot 10^{-3}$ M) and crystallizes during cooling of the acetylene-containing mixture to 20°C , has the form of large (up to 5 cm in diameter) very thin plates. Under similar conditions without acetylene, a mechanical mixture of prisms (3-5 mm in length) of approximate composition oxime:KOH = 3:1 and KOH precipitated. It is assumed [3] that in the first case a complex acetylene-KOH-DMSO complex is formed which has increased basicity and reacts more actively with the oxime. At the reaction temperature, potassium oximate is only partially soluble in DMSO, which subsequently was taken into account in calculations of the rate constants. In addition to the formation of potassium oximate, very small peaks of intermediates were observed in the GLC chromatograms in only two cases. On the basis of the retention time, these were hydroxypyrroline ($<2\%$ of the concentration of the starting oxime in the case of cyclohexanone oxime) and O-vinyl oxime ($<5\%$ in the case of 4-methylcyclohexanone oxime). The maximum concentrations of the intermediates coincided in time with the moment of attainment of the maximum rate of formation of the corresponding pyrroles.

With allowance for the constant acetylene concentration, the rate constants for various steps of formation of vinylpyrroles from oximes was calculated according to the simplified reaction scheme



The concentration of potassium oximate in DMSO was taken in the calculations of k_1 . The obtained results are given in Table 1. On the basis of the values of k_1 , the effect of the ring size is expressed most strongly in the step of the reaction of potassium oximate with acetylene and only insignificantly in the vinylation step (k_2).

From Fig. 1 and Table 1, it is evident that not only N-vinylpyrroles, but also pyrroles can be synthesized selectively from cycloheptanone and cyclooctanone oximes (the optimum synthesis time is ~3 h). Confirming this, we obtained 4,5,6,7,8,9-hexahydro-1H-cycloocta[b]pyrrole, having stability lower than that of other cyclic homologs, which may be the reason for the unsuccessful attempt to synthesize this compound from cyclooctanone oxime and acetylene [2]. Vinylation of cycloalka[b]pyrroles at atmospheric pressure occurs more than an order slower than pyrrole formation (see Fig. 1 and Table 1); therefore, for preparative production of the corresponding N-vinylpyrroles from oximes, it is appropriate to carry out the reaction under acetylene pressure (in an autoclave). The yields of the target products at moderate reaction temperature ($\sim 90^\circ\text{C}$) are close to quantitative.

In conclusion, we should note that the rate constants discussed above reflect the kinetic picture only for given concentrations of alkali and water in DMSO. The effect of the latter substances on the reaction was discussed previously [1, 4].

EXPERIMENTAL

The synthesis of N-vinylpyrroles was carried out in a 25-ml reactor into which had been placed 15 ml of a solution of the cycloalkanone oxime (0.47 M) in DMSO containing 0.2% H₂O and an amount of KOH equivalent to that of the oxime. The mixture was stirred with a magnetic stirring device ($n = 1500$ rpm), and a heat-transfer agent with a preassigned temperature (86°C) was fed into the reactor jacket from a controlled-temperature vessel. After the reaction material attained the temperature, acetylene was fed (time $t = 0$ and $P_{C_2H_2} = 720$ mm), samples of the supernatant solution were withdrawn through a rubber membrane at specific time intervals (with the stirring device disconnected), and the samples were analyzed by GLC. The time for establishment of an equilibrium acetylene concentration at the reaction temperature did not exceed 30 sec. The concentrations of the reaction products were found according to the readings of an ITs-26 electronic integrator using the data of preliminary calibration. The internal standard was the solvent DMSO. The total concentration of the oxime in the reaction mixture (the oxime + the potassium oximate that dissolved and was found in the precipitate) was calculated from the material balance because the yields of the final N-vinylpyrroles were practically quantitative (see Table 1). The constants k_1 were calculated by dividing the maximum rate of consumption of the corresponding oximes by the concentration of potassium oximate in the solution, with the rate having been obtained from data of potentiometric titration of the supernatant liquid (in the KOH precipitate and part of the potassium oximate), and the constants k_2 were obtained by dividing the maximum rate of formation of N-vinylpyrroles by the maximum concentration of pyrroles [5].

The crystalline oximates were obtained by cooling an equimolar mixture of cyclohexanone oxime and KOH (each 0.47 M) from 86 to 20°C in DMSO for 2 h after preliminary stirring for 0.5 h both with the acetylene and without it. The crystals were filtered, washed with ether, and dried, and the composition was analyzed by potentiometric titration. Because excess KOH was found in the precipitate, crystals were taken from the upper part of the mixture for the analysis. Without KOH, the cyclohexanone oxime was completely soluble (0.47 M in DMSO) at room temperature.

Below we describe preparative syntheses of cycloalka[b]pyrroles and their N-vinyl derivatives not obtained previously by the method of [1].

4,5,6,7,8,9-Hexahydro-1H-cycloocta[b]pyrrole from Cyclooctanone Oxime. The reaction (see above) was terminated after 3 h. The mixture was cooled to 20°C. The N-vinyl derivative was separated by extraction with hexane. The pyrrole was extracted with ether after dilution with water, and the unreacted cyclooctanone oxime was washed with a 50% aqueous KOH solution. The ether extracts were washed with water and dried with Na₂SO₄ under argon. After distillation of the ether and vacuum treatment, the pyrrole was obtained in 60% yield on the basis of the reacted cyclooctanone oxime and had purity 96.4% and bp 57-58°C ($5 \cdot 10^{-2}$ mm). The spectral characteristics corresponded to the data of [2].

1-Vinyl-4,5,6,7,8,9-hexahydro-1H-cycloocta[b]pyrrole. Into a rotating 0.5-liter steel autoclave were placed 3.6 g (25.5 mmoles) of cyclooctanone oxime and 1.43 g of KOH (25.5 mmoles) in 50 ml of DMSO. Acetylene was fed until saturation ($P_{C_2H_2} = 12$ atm), and the reaction was carried out for 5 h at 80-90°C. After cooling, the obtained mixture was discharged and diluted twofold with water, the product was extracted with ether (5×30 ml), and the ether extracts were washed with water, dried with Na₂SO₄, and passed through an Al₂O₃ bed for clarification. The target pyrrole was obtained in quantitative yield (4.47 g, 25.5 mmoles) with bp 64.5-66°C ($3 \cdot 10^{-2}$ mm), d_D^{20} 0.9809, and n_D^{20} 1.5512 by distillation of the ether with subsequent vacuum treatment. Proton NMR spectrum (CDCl₃, δ , ppm): 1.3-1.6 multiplet (8H), 2.5-2.7 multiplet (4H), 4.50 quartet (1H), 4.96 quartet (1H), 5.92 doublet (1H), 6.81 quartet (1H), 6.88 doublet (1H). Carbon-13 NMR spectrum (CDCl₃, δ , ppm): 22.27, 25.84, 2×26.11 , 28.93, 31.75, 96.54, 110.52, 114.37, 122.05, 128.99, and 130.56.

1-Vinyl-4,5,6,7,8,9,10,11,12,13-decahydro-1H-cyclododeca[b]pyrrole. The synthesis and treatment were similar to the preceding. From 25 mmoles of cyclododecanone oxime, 25 mmoles of the corresponding N-vinylpyrrole was obtained with bp 114-116°C ($5 \cdot 10^{-2}$ mm) and n_D^{20} 1.5472. Proton NMR spectrum (CHCl₃, δ , ppm): 1.25-1.65 multiplet (16H), 2.36 multiplet (2H), 2.61 multiplet (2H), 4.55 quartet (1H), 4.99 quartet (1H), 6.03 doublet (1H), 6.86 quartet (1H), 6.91 doublet (1H); in the vinyl group $J_{trans} = 15.6$, $J_{cis} = 8.9$, and $J_{gem} = 0.6$ Hz; in the pyrrole ring $J = 3.1$ Hz. Carbon-13 NMR spectrum (CDCl₃, δ , ppm): 20.82, 22.47, 2×22.80 , 24.11, 24.90, 25.08, 25.30, 28.07, 29.04, 96.42, 110.09, 115.54, 121.20, 122.78, and 131.25.

The GLC analysis was carried out with an LKhM-80 instrument, potentiometric titration was carried out with an OP-208 pH meter, and the NMR spectra were recorded on Tesla BS-567 A (100 MHz, ^1H) and Bruker WP-200sy (200 MHz, ^1H and 50.33 MHz, ^{13}C) spectrometers.

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INTERACTION OF VICINAL N-METHYL AND C²-ISOPROPYL SUBSTITUENTS IN 3-KETOPIPERIDINES: RING CONFIGURATION AND STEREOCHEMISTRY OF CARBONYL REACTIONS

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The cis- and trans-1,5-dimethyl-2-isopropyl-3-piperidones were synthesized. Their configurations were determined using ^1H and ^{13}C NMR spectroscopy. The stereochemistry of the hydride and catalytic reduction of the resulting 3-piperidones was studied.

Previously, using N-tert-butyl substituted 3- and 4-ketopiperidines it had been shown that there is a strong steric interaction between a bulky substituent on the nitrogen atom

TABLE 1. Chemical Shifts and Splitting Constants for Isomers of Ketones (IIIa) and (IIIe)

trans-(IIIe) in C ₆ D ₆			cis-(IIIa) in CDCl ₃		
Protons	δ , ppm	J, Hz	Protons	δ , ppm	J, Hz
C ⁵ -CH ₃	0,545 d	$J_{\text{CH}_3-\text{H}}=6.0$	C ⁵ -CH ₃	0,88d	$J=6,5$
C ⁷ (CH ₃) ₂	0,98 d 1,045 d	$J_{\text{CH}_3-\text{H}}=6.8$	C ⁷ (CH ₃) ₂	0,72d 0,97d	$J=6,3$
C ⁴ H _a	1,585 d.d.d	$J_1=12,7, J_2=10,5, J_3=1$	C ⁷ -H	2,04 m	
C ⁷ (CH ₃) ₂	1,99 m		C ⁴ H _a	2,06 d.d	$J_1=13, J_2=11,9$
N-CH ₃	2,0 s		C ² H	2,0 m	
C ⁶ H _a +HC ⁵	2,1 m		C ⁴ H _e	2,23 d.d.t	$J_1=13, J_2=4,5, J_3=1,5$
C ⁴ H _e	2,23 m		N-CH ₃	2,40 s	
C ² H	2,45 d.d	$J=7,6$	C ³ H	2,47m	
C ⁶ H _a	2,545 m		C ⁶ H _e	2,55 m	
			C ⁶ H _a	2,84d.d	$J_1=13,5, J_2=11,2$

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