PYRROLES FROM KETOXIMES AND ACETYLENE.

19.* REGIOSELECTIVITY OF THE REACTION OF ALKYL BENZYL KETOXIMES WITH ACETYLENE

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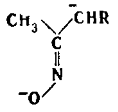
Alkyl benzyl ketoximes react with acetylene at 60-150°C in MOH—dimethyl sulfoxide (M = Li, K) primarily by means of the methylene group of the benzyl grouping, which is primarily anti-oriented with respect to the hydroxy group, to give 2-alkyl-3-phenylpyrroles in greater than 70% yields. The specific participation of the anti-methylene group in the construction of a pyrrole ring constitutes evidence against mechanisms that include a [3,3]-sigmatropic shift in O-vinyl oximes. It follows from the results obtained that the reaction proceeds through an anti-dianion of the benzyl type stabilized by conjugation with the aromatic ring.

The question of regiospecificity is of fundamental importance in the systematic development of a new synthesis of pyrroles from ketoximes and acetylene in the KOH—dimethyl sulfoxide (DMSO) superbase system [2-4], since it is directly associated with elucidation of its mechanism. We have previously shown [5] that unsymmetrical methyl alkyl ketoximes $CH_3C(=NOH)-CH_2R$ (where R = alkyl) provide exclusively their methylene groups for the formation of a pyrrole ring in the case of reaction with acetylene at up to 120°C. To the probable reasons for such regiospecificity examined in [5] it would seem that one could add, at first glance, the relatively high stability of anti-dianion A as compared with alternative syn-dianion B, in which repulsion of the closely situated charges should be stronger.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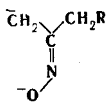
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However, there is evidence [6] that syn-dianion B is at least substantially more stable than anti-dianion A, although Jung and co-workers were unable to obtain disodium and dipotassium salts of the ketoximes.

The methyl group also begins to participate in the formation of the pyrrole ring at higher temperatures (140°C); this may be associated with a shift of the configuration equilibrium (syn $\rightleftarrows$ anti), since unsymmetrical ketoximes usually have a similarly syn orientation of the OH group with respect to the least bulky substituent.

For the further study of the regiospecificity of the reaction we selected methyl and ethyl benzyl ketoximes (I, II); the former was obtained in the form of the pure syn isomer (Table 1), while the latter was obtained as a mixture of syn and anti isomers in a ratio of ~45:55 (Table 2). Tables 1 and 2 show that at room temperature solvents that differ fundamentally with respect to their solvation properties have virtually no effect on the configuration ratios. When oxime I is heated in nitrobenzene for 1 h, it undergoes partial conversion to the anti isomer, the fraction of which increases with the temperature (according to the PMR data): from ~1% at 25°C to 36% at 150°C.

In the KOH—DMSO system oxime I is converted to a mixture of syn and anti isomers (74:26) even in the case of brief heating (at ~80°C for 10 min); a further increase in the temperature

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*See [1] for communication 18.

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TABLE 1. Chemical Shifts of the Protons of syn-Methyl Benzyl Ketoxime[a] in Various Solvents (δ, ppm, 20% solutions by volume)

Solvent	CH_3	CH_2	Ph	OH
CCl_4[b]	1,76	3,45	7,17	10,15
$CHCl_3$	1,77	3,46		10,12
CD_3OD	1,70	3,41		
PhH[c]	1,63	3,27		10,47
$PhNH_2$	1,61	3,26		
$PhNO_2$	1,75	3,46		
DMSO	1,67	3,43	7,20	10,45

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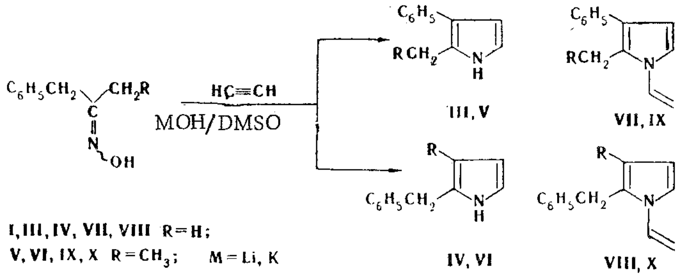
[a] In the spectrum of a solution in $PhNO_2$ we observed a weak CH_2 signal (3.70 ppm), which, according to [7], can be assigned to the anti isomer (~1%). [b] In [7] in the spectrum of a solution in this solvent (50% solution) two isomers (syn:anti = 74:26) with CH_3 and CH_2 chemical shifts of 1.80 and 3.51 (syn) and 1.80 and 3.76 ppm (anti), respectively, were observed. [c] According to the data in [7], in the spectrum of a 10% solution two isomers with CH_3 and CH_2 chemical shifts of 1.73 and 3.39 (syn) and 1.63 and 3.71 ppm (anti) were found.

(to 150°C) has virtually no effect on the isomer ratio, which later remains the same at room temperature also. Consequently, the percentage of the anti form in oxime I, which ranges from 26% to 36% (depending on the medium), is evidently close to the equilibrium value. In contrast to oxime I, the ratio of the isomers in a starting sample of oxime II apparently already corresponds to the equilibrium value, since it remains almost unchanged in the case of heating in nitrobenzene (150°C) or KOH–DMSO (170°C).

In the reaction of oximes I and II with acetylene in each case one might have expected the formation of two structurally isomeric pyrroles (III, IV, and V, VI) and their N-vinyl derivatives VII-X, which differ with respect to the position and structure of the substituents in the ring:



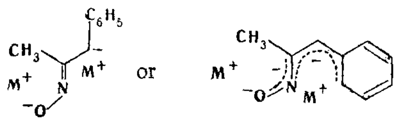
However, only N-vinylpyrrole VII is present in the products of the reaction of methyl benzyl ketoxime (I) with excess acetylene (100°C, KOH), as evidenced by analysis by gas-liquid chromatography (GLC) and the PMR spectra. The regiospecifity of the reaction is not disrupted even under more severe conditions (120°C), and the structurally isomeric N-vinylpyrrole VIII was not observed in the reaction mixture. A similar result was obtained when the reaction was carried out in an LiOH–DMSO system (120°C), which catalyzes the vinylation step less actively. Under these conditions N-vinylpyrrole VII and its nonvinylated precursor III are formed in approximately equal amounts (1:1.2). Their structural isomers VIII and IV are absent in the reaction mixture. A peculiarity of the reaction under the influence of the LiOH–DMSO system is the more clearly expressed (than in the case of KOH) deoximation process — the formation of the starting ketones, which are readily identifiable in the reaction mixture by IR spectroscopy from the band at 1710 cm^{-1}, which is absent in the spectra of the oximes. At increased concentrations of the reagents and the base (9% of the oxime and 3.5% KOH based on the weight of the reaction mixture instead of 7% and 2.5%, respectively) and when we carried out the reaction at 120°C, we were able to also isolate and characterize by spectral methods (Tables 3 and 4) pyrrole IV, i.e., the methyl group also begins to react under the given conditions.

The results obtained constitute evidence that ketoxime I reacts with acetylene primarily by means of the methylene group of the benzyl grouping, which exists primarily in an anti

TABLE 2. Chemical Shifts of the Protons of the syn and anti Isomers of Ethyl Benzyl Ketoxime in Various Solvents (δ, ppm, 20% solutions by volume)

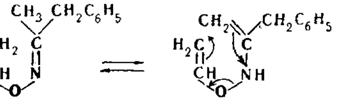
Solvent	CH_3	CH_2	CH_2Ph	Ph	OH
CCl_4	1,01; 0,93	2,13; 2,25	3,69; 3,45	7,19	
$CHCl_3$	0,96; 0,89	2,10; 2,26	3,70; 3,45		10,44; 10,44
CD_3OD	0,95; 0,88	2,09; 2,23	3,69; 3,43		
PhH	0,83; 0,81	1,95; 2,23	3,63; 3,32		
$PhNO_2$	0,93; 0,90	2,11; 2,28	3,72; 3,49		
DMSO			3,63; 3,43		10,57; 10,46

orientation with respect to the hydroxy group, i.e., the reaction in this case proceeds through an anti-dianion of the benzyl type, which is stabilized by conjugation with the aromatic ring:



Ketoxime II reacts with excess acetylene in the KOH–DMSO system at 100°C to give two isomeric N-vinylpyrroles (IX and X); as the temperature is raised, the fraction of vinylpyrrole IX, which is formed through the benzyl group, decreases appreciably (from 85% at 100°C to 45% at 150°C). A further increase in the reaction temperature gives rise to resinification and a sharp decrease in the overall yield of N-vinylpyrroles. At 60-80°C the principal reaction product is nitrogen-unsubstituted pyrrole V. For example, a mixture of isomeric pyrroles V and VI in a ratio of 5.7:1 (according to the PMR data) was obtained at 80°C. Thus ketoxime II reacts with acetylene primarily by means of the methylene group of the benzyl grouping.

However, under comparable conditions (100°C) the overall yield of N-vinylpyrroles IX and X (37%) is half the yield of N-vinylpyrrole VII, which is formed from oxime I. Since the latter is primarily the syn isomer, in contrast to oxime II, which is an equimolar mixture of syn and anti isomers, this result once again indicates that the benzyl group, which is anti-oriented with respect to the hydroxy group, primarily undergoes reaction. The specific participation of the anti-methylene group in the construction of a pyrrole ring constitutes evidence against mechanisms that include a [3,3]-sigmatropic shift in O-vinyl oximes — possible reaction products.



If the formation of pyrroles were to take place via this pathway, the structural specificity of the reaction would be the opposite of the observed specificity. We were able to isolate O-vinyl oximes in low yields from the products of the reaction of acetylene with some lower dialkyl ketoximes [8]. At temperatures above 100°C they decompose readily; however, in contrast to O-1,2-dicarbomethoxyvinyl oximes [9], pyrroles are not formed in this case.

EXPERIMENTAL

Analysis by GLC was carried out with a KhL-6 chromatograph with catharometer as the detector; the column length was 2.5 m, the column diameter was 3 mm, the solid phase was Chromaton N-AW-DMCS, the liquid phase was 10% DS-550 silicone, the thermostat temperature was 180°C, and the carrier gas was helium. The IR spectra of thin films (IV, VII, and IX) and KBr pellets (III) of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of 10% solutions of the compounds in CCl_4–hexamethyldisiloxane (HMDS) were obtained with a BS-487B spectrometer (80 MHz). The PMR spectra of the oximes were obtained with a Varian XL-100/12 spectrometer.

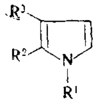
Oxime I was obtained from the Angarsk chemical reagent plant and had mp 65-67°C (mp 68-70°C [10]). Oxime II was synthesized by the method in [11], modified as described below.

Ethyl Benzyl Ketoxime (II). A three-necked flask equipped with a stirrer and a ball-type condenser was charged with 22.4 g (0.32 mole) of hydroxylamine hydrochloride, 160 ml of

TABLE 3. IR Spectra of the Pyrroles

Compound	Characteristic frequencies, cm^{-1}
III	515, 650, 700, 714, 764, 897, 956, 1030, 1086, 1256, 1375, 1445, 1510, 1604, 2855, 2916, 3025, 3055, 3380, 3426
IV	407, 540, 717, 767, 885, 957, 1028, 1092, 1108, 1378, 1452, 1495, 1580, 1604, 2858, 2930, 2960, 3025, 3060, 3083, 3390, 3426
VII	505, 590, 620, 662, 700, 715, 765, 862, 910, 957, 1032, 1072, 1130, 1147, 1248, 1300, 1320, 1372, 1380, 1437, 1458, 1500, 1560, 1578, 1604, 1642, 2852, 2922, 2952, 3030, 3055, 3080
IX	700, 735, 767, 927, 957, 1032, 1072, 1250, 1331, 1380, 1424, 1452, 1489, 1502, 1602, 1642, 2877, 2930, 2971, 3034, 3063

TABLE 4. PMR Spectra of the Pyrroles



Compound	δ, ppm										
	R^1	R^2	R^3	H_A[a]	H_B[a]	H_C[a]	3-H	4-H	5-H	Me	CH_2
III	H	Me	Ph					6,14	6,35	2,05	
IV	H	$PhCH_2$	H				5,85	5,95	6,42		3,85
VII[b]	$CH{=}CH_2$	Me	Ph	5,00	4,57	6,85		6,15	6,85	2,27	
IX[b]	$CH{=}CH_2$	Et	Ph	5,03	5,59	6,86		6,14	6,82	1,10	2,70
X[b]	$CH{=}CH_2$	$PhCH_2$	Me	4,85	4,36	6,60		5,93	6,80	2,00	3,90

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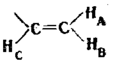
[a] Protons of the vinyl group: 

. [b] In this case $^2J_{AB}$ = 0.8, $^3J_{AC}$ = 15.8, and $^3J_{BC}$ = 8.9 Hz. For all of the pyrroles $^3J_{45} \simeq 2.0$ Hz.

ethanol, 20 ml of water, and 30 g (0.2 mole) of ethyl benzyl ketone, and 8 g (0.2 mole) of NaOH in 20 ml of water was added gradually with continuous stirring. The mixture was then heated at 65-70°C for 2 h, after which it was cooled and poured into 500 ml of acidified water. The oxime was extracted with ether, the ether extracts were washed with water and dried with potassium carbonate, and the ether was removed. The residue was fractionated *in vacuo* to give 25 g (76%) of oxime II in the form of a yellowish liquid that was not very mobile and had bp 120-122°C (6 mm). Found: C 73.2; H 7.8; N 8.5%. $C_{10}H_{13}NO$. Calculated: C 73.6; H 8.0; N 8.6%.

2-Methyl-3-phenylpyrrole (III), 2-Benzylpyrrole (IV), and 1-Vinyl-2-methyl-3-phenylpyrrole (VII). A) A mixture consisting of 7.4 g (0.05 mole) of oxime I, 2.8 g (0.05 mole) of KOH, and 100 ml of DMSO was heated at 100°C in a 1-liter steel rotating autoclave with acetylene (initial pressure 14 atm) for 3 h. Water (500 ml) and ~10 g of NaCl were then added to the reaction mass, and the mixture was extracted with ether. The extract was washed with water and dried with potassium carbonate, and the ether was removed. The residue was fractionated *in vacuo* to give 6.7 g (74%) of vinylpyrrole VII with a purity of 99.9%, bp 124°C (1.5 mm), D_4^{20} 1.0345, and n_D^{20} 1.6009. Found: C 85.0; H 7.2; N 8.1%. $C_{13}H_{13}NO$. Calculated: C 85.0; H 7.1; N 7.5%. The IR and PMR spectra are presented in Tables 3 and 4.

B) At 120°C and under the same other conditions 5.9 g (65%) of vinylpyrrole VII was obtained.

C) The reaction at 120°C in 70 ml of DMSO and under the same other conditions gave 4.6 g of a mixture consisting of three pyrroles. Column chromatography [L 100/250 silica gel, hexane—ether (3:1)] gave 0.1 g (1%) of 2-benzylpyrrole VI, 0.9 g (12%) of vinylpyrrole VII, and 2.2 g (28%) of pyrrole III, which was contaminated with starting oxime I. Additional distillation of pyrrole III *in vacuo* gave 1.6 g of a pure substance — a light-yellow liquid [bp 124°C (2 mm)] that turned red instantly in air and crystallized to give a product with mp 25-27°C (from petroleum ether). See Tables 3 and 4 for the spectra of pyrroles III and IV.

D) The reaction at 120°C in the presence of 1.2 g (0.05 mole) of LiOH under the same other conditions gave 2.2 g of a mixture of pyrrole III and vinylpyrrole VI (1:1). Chromatography with a column [L 100/250 silica gel, hexane—ether (3:1)] gave 0.7 g (~8%) of vinylpyrrole VII and 0.9 g (12%) of pyrrole III.

1-Vinyl-2-ethyl-3-phenylpyrrole (IX). A) The reaction of 8.1 g (0.05 mole) of oxime II by method A (see above) gave 4.1 g (37%) of a mixture of isomeric vinylpyrroles IX and X in a ratio of 6:1 (GLC) with bp 110-115°C (1.5 mm). See Tables 3 and 4 for the spectrum of pyrrole IX and Table 4 for the spectrum of pyrrole X.

B) The reaction at 120°C under the same other conditions gave 4 g (35%) of a mixture of vinylpyrrole IX and X (IX:X = 5:1 according to GLC).

C) The reaction of 2 g (0.012 mole) of oxime II and 0.7 g (0.012 mole) of KOH in 25 ml of DMSO at 80°C for 1 h with acetylene in an autoclave (initial pressure 12 atm) gave, after workup as described above, 1.5 g (71%) of a mixture consisting of pyrroles V and VI in a ratio of 5.7:1 (PMR). See Table 4 for the PMR spectra of pyrroles V and VI.

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