ISOMERIC COMPOSITION OF PYRAZOLINES OBTAINED FROM UNSATURATED CARBONYL COMPOUNDS AND HYDRAZINE

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The Δ^2-pyrazolines synthesized under the usual conditions from unsaturated aldehydes and hydrazine contain from 2 to 3% of the Δ^1-isomers and considerable amounts of the isomeric 3-alkyl-Δ^2-pyrazolines, which are formed as a consequence of migration of the double bond. Mixtures of the stereoisomeric Δ^2-pyrazolines are formed from α,β-dialkyl-substituted acroleins. Migration of the double bond does not occur in the condensation of unsaturated ketones with hydrazine, and Δ^2-pyrazolines that are free from admixtures of the structural isomers are obtained.

In studies conducted in the last five years [1,2], it was established that the formation of mixtures of structurally isomeric Δ^2-pyrazolines often occurs in the condensation of α,β-unsaturated aldehydes with monoalkylhydrazines, the probable reason for which is the steric hindrance to the addition of the NH group of the alkylhydrazine to the substituted C=C bond and the possibility of the attack of NH by the carbonyl group [3]. In the case of the reactions of hydrazine itself with unsaturated carbonyl compounds, such reasons for the formation of isomeric pyrazolines are excluded, but one cannot exclude the possibility of the formation of isomers due to migration of the double bond in the pyrazole ring. Examples of this sort of a longer $\pi-\pi$ conjugated system have long been known. Thus as early as 1924 it was established that the condensation of hydrazine with 3,4-dimethoxycinnamaldehyde gives the 3-substituted isomer rather than the expected 5-aryl-substituted Δ^2-pyrazoline [4], and a mixture of 5- and 3-phenyl-Δ^2-pyrazolines was later obtained from cinnamaldehyde [5]. However, the possibility of the migration of a double bond under the conditions of the synthesis of the simplest pyrazolines with alkyl substituents (in the absence of $\pi-\pi$ conjugation effects) required a special investigation. The isomerization of 5-methyl-Δ^2-pyrazoline to 3-methyl-Δ^2-pyrazoline was recently accomplished under comparatively severe conditions (heating to 180° with KOH) [6], but conversion of 5,5-dimethyl-Δ^2-pyrazoline to the Δ^1-isomer proved to be unexpectedly easily brought about even on distillation [7].

In the old investigations of the synthesis of pyrazolines, the admixture of isomers was not monitored because of the absence of suitable analytical methods, and there is no information regarding the percentage of isomers in the products of the condensation of hydrazine with unsaturated aldehydes and ketones. We investigated the isomeric composition of pyrazolines formed in the cold from hydrazine hydrate and unsaturated carbonyl compounds $C_4H_6O-C_6H_{10}O$ (crotonaldehyde, tiglaldehyde, α-methyl-, α-ethyl-, and α-methyl-β-ethylacroleins, methyl vinyl ketone, methyl isopropenyl ketone, and mesityl oxide). It turned out that only the 3-alkyl-substituted pyrazolines obtained from the unsaturated ketones are structurally homogeneous: they contained neither Δ^1-pyrazolines nor Δ^2-pyrazolines with side chains in a different position relative to the C=N bond, which might have been formed as a consequence of migration of the latter. On the other hand, appreciable amounts of both the Δ^1-pyrazoline and isomeric 3-substituted Δ^2-pyrazolines are present along with the chief product—the Δ^2-pyrazoline of the appropriate structure—in the reaction mixtures from the condensation of several unsaturated aldehydes with hydrazine hydrate (Table 1). Since the starting unsaturated aldehydes did not contain impurities, the presence of isomers can be explained by the comparatively facile isomerization of the Δ^2-pyrazoline to the Δ^1-isomer with subsequent conversion to 3-alkyl-Δ^2-pyrazoline. This isomerization is catalyzed by bases, so that the amount of isomers depends on the time and method used in the treatment of the reaction mixtures. As seen from the data in Table 1,

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TABLE 1. Ratio of Isomeric Pyrazolines in the Products of the Condensation of Unsaturated Aldehydes with Hydrazine Hydrate (in %)

Position of the alkyl substituents	Δ^2	Δ^1	3-Alkyl-Δ^2	Drying agent (drying time, h)
4-Methyl	99,4	0,6	—	K_2CO_3 (12)
4-Methyl	98,2	1,8	—	K_2CO_3 (48)
4-Methyl	98,9	1,1	—	KOH (12)
4-Methyl	97,9	2,1	—	KOH (48)
5-Methyl	95,2	2,7	2,2	KOH (12)
5-Methyl	90,0	3,3	6,7	KOH (48)
5-Methyl	99,1	0,3	0,6	K_2CO_3 (12)
5-Methyl	97,3	0,1	2,6	K_2CO_3 (48)
4-Ethyl*	95,8	2,0	—	K_2CO_3 (24)
4,5-Dimethyl	78,4	1,7	19,9	K_2CO_3 (72)
4,5-Dimethyl	93,1	0,9	5,9	K_2CO_3 (24)
4-Methyl-5-ethyl	51,0	1,5	47,5	K_2CO_3 (~1month)

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* The mixture contained 2.2% of an unidentified component.

TABLE 2. Properties of Δ^2-Pyrazolines

Name	bp, °C (mm)	d_4^{20}	n_D^{20}	n_C^{20}	Δ_{FC}^{20}	ω_{FCD}	MR_D found	MR_D calc.[a]	$\nu_{C=N}$, cm^{-1}	ν_{NH}, cm^{-1}	λ_{max} nm (ε)[b]	Yield, %
4-Methyl-Δ^2-pyrazoline[c]	36,5—38,1 (6)	0,9730	1,4749	1,4716	118,6	24,97	24,33	24,70	1591	3310	234 (3200)	49
4-Ethyl-Δ^2-pyrazoline[d]	72,8—74,0 (20)	0,9541	1,4743	1,4709	103,0	21,64	28,91	29,35	1590	3300	232 (2500)	53
5-Methyl-Δ^2-pyrazoline[e]	40,5—42,0 (9)	0,9692	1,4725	1,4693	99,7	21,01	24,30	24,70	1598	3300	229 (3300)	46
4,5-Dimethyl-Δ^2-pyrazoline (27% trans + 73% cis)[f]	63,4—64,5 (20)	0,9448	1,4687	1,4657	110,4	23,56	28,90	29,35	1593	3305	234 (3300)	42
4-Methyl-5-ethyl-Δ^2-pyrazoline (60% trans + 40% cis)[g]	74,6—75,6 (20)	0,9230	1,4659	1,4629	107,8	23,14	33,66	34,00	1590	3300	234 (3300)	44

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[a] From Vogel's bond refractions.

[b] In alcohol solutions (data of L. M. Korzhikova).

[c] bp 142-145° (733 mm) [12].

[d] Found %: N 28.6. $C_5H_{10}N_2$. Calculated %: N 28.5.

[e] bp 50-55° (20 mm) [6].

[f] Found %: N 28.7. $C_5H_{10}N_2$. Calculated %: N 28.5.

[g] The only information available on the boiling point of this pyrazoline (105-107° at 18 mm) [13] is apparently incorrect.

TABLE 3. Relative Retention Times of Δ^1- and Δ^2-Pyrazolines on Cyanoethylated Mannitol

Position of the alkyl substituents	τ_{rel} $(\Delta^1 : \Delta^2)$
4-Methyl	0,47
4-Ethyl	0,45
5-Methyl	0,47
cis-4,5-Dimethyl	0,47
trans-4,5-Dimethyl	0,53
cis-4-Methyl-5-ethyl	0,54
trans-4-Methyl-5-ethyl	0,57

after prolonged drying with potassium carbonate and, particularly, potassium hydroxide, the reaction mixtures contain from several percent to several tens of percent of the isomers.

The results are of interest as characteristic of the comparative stability of isomeric pyrazolines and for the synthesis of pure pyrazolines. Although the numbers in Table 1 are, of course, not the equilibrium concentrations, they are evidence that the less stable isomers – the Δ^1-pyrazolines – should nevertheless be present at equilibrium in amounts of several percent, while the 3-alkyl-substituted Δ^2-pyrazolines are much more stable than the corresponding Δ^1-pyrazolines and isomeric 5-substituted compounds. The rate of isomerization of the pyrazolines apparently depends substantially on their structure, and the absence of isomeric impurities in the 3-alkyl-Δ^2-pyrazolines obtained from ketones is apparently explained not only by their much higher thermodynamic stability but also by the very low rate of isomerization. Owing to this, Δ^2-pyrazolines with a side chain in the 3 position are obtained in pure form from the corresponding unsaturated ketones, but thorough removal of the isomers formed (especially in the case of 5-alkyl-substituted compounds, which are comparatively readily converted to 3-substituted compounds) is necessary in the synthesis of pyrazolines from unsaturated aldehydes and hydrazine.

The formation of stereoisomeric pyrazolines is possible in two of the examined reactions. The results of gas-chromatographic analysis and the PMR spectra of the products of the condensation of hydrazine with tiglaldehyde and α-methyl-β-ethylacrolein demonstrate that they contain mixtures of cis and trans isomers. 4,5-Dimethyl-Δ^2-pyrazoline consisted of 73% cis and 27% trans forms, while 4-methyl-5-ethyl-Δ^2-pyrazoline contained 40 and 60% of the corresponding stereoisomers. According to the most recent views [8], the stereoisomeric composition of 4,5-disubstituted pyrzolines obtained from α,β-unsaturated carbonyl compounds should be determined by the stereochemistry of the protonation of the intermediate Δ^3-pyrazolines and the possibility of the establishment of equilibrium between the stereoisomers. The data available up to now [1,8-10] pertained to the stereoisomerism of 1-substituted Δ^2-pyrazolines synthesized from phenylhydrazine and methylhydrazine. Our data complement this information and demonstrate that, in all of the cases studied, the 4,5-disubstituted pyrazolines obtained from unsaturated carbonyl compounds contain both stereoisomeric forms, the ratio between which varies over rather wide limits.

The literature data on alkyl-substituted Δ^2-pyrazolines are inadequate and in most cases pertain to preparations of an uncertain degree of purity. The characteristics of twice-distilled, chromatographically pure Δ^2-pyrazolines are presented in Table 2.

EXPERIMENTAL

Condensation of Unsaturated Carbonyl Compounds with Hydrazine. This was carried out under standard conditions without a solvent. An equimolar amount of freshly distilled, chromatographically pure carbonyl compound was added with stirring and ice cooling to 96% hydrazine hydrate (0.5-2 mole) at such a rate that the temperature of the reaction mixture did not exceed 10-15°. The mixture was then stirred for 1 h at room temperature, powdered potassium carbonate was added, and the mixture was stirred for another hour. The organic layer was dried for a certain time over granulated potassium carbonate or alkali, analyzed with a chromatograph, and then distilled with a vacuum column (15 theoretical plates) in a stream of nitrogen.

Chromatographic Analysis. This was carried out with a Tswett-1 chromatograph with a metric glass column containing Celite-545 (60-80 mesh) with 10% cyanoethylated mannitol. The column temperature was 100°, and the carrier gas was nitrogen.

The Δ^1-pyrazolines always had shorter retention times than the corresponding Δ^2-isomers, which do not have substituents in the 3 position, while the 3-alkyl-Δ^2-pyrazolines always had longer retention times than the latter. The monoalkyl-Δ^1-pyrazolines were identified by mixing with authentic preparations prepared by isomerization of Δ^2-pyrazolines [11]. 3-Methyl- and 3,4-dimethyl-Δ^2-pyrazolines were identified with genuine preparations obtained from methyl vinyl ketone and methyl isopropenyl ketone, respectively.

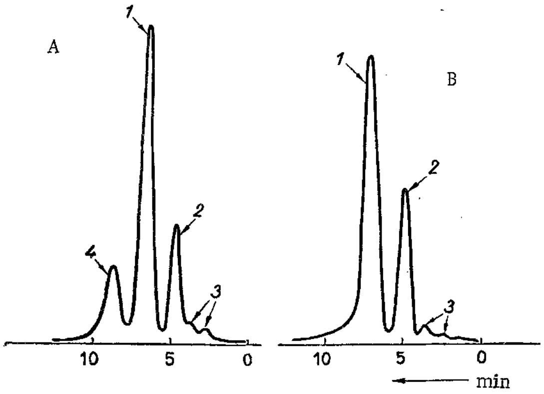

Fig. 1. Chromatograms of the reaction mixture of products of the condensation of hydrazine hydrate with tiglaldehyde (A) and of the 4,5-dimethyl-Δ^2-pyrazoline (B) isolated from it: 1) and 2) cis- and trans-4,5-dimethyl-Δ^2-pyrazolines (respectively); 3) cis- and trans-3,4-dimethyl-Δ^1-pyrazolines; 4) 3,4-dimethyl-Δ^2-pyrazoline.

In the case of 4,5-dialkylpyrazolines, the peaks of the Δ^1-isomers were assigned from the retention times, since it turned out that the ratio of the retention times ($\Delta^1 : \Delta^2$) was approximately constant and averaged 0.5 (see Table 3). For $\tau_{rel} \approx 0.5$, there were two peaks on the chromatogram of the reaction mixture from the synthesis of 4,5-dialkyl-Δ^2-pyrazolines, and we assigned them to the cis- and trans-3,4-dialkyl-Δ^1-pyrazolines. By way of illustration, the chromatogram of the reaction mixture of 4,5-dimethylpyrazolines is presented in Fig. 1. The identification of the major components as cis and trans forms of 4,5-dimethyl-Δ^2-pyrazoline was made on the basis of the PMR spectrum, which is the superimposition of signals of these stereoisomers with approximately the same intensity ratio as for the major peaks on the chromatogram. The multiplets of the $H-C^5$ and $H-C^4$ protons of the trans form (τ 6.72 and 7.45 ppm) are situated at higher field than the corresponding multiplets of the cis form (τ 6.27 and 7.10 ppm), while the doublets of the methyl groups of the trans form (CH_3C^5 and CH_3C^4), on the other hand, have lower τ values (8.72 and 8.82 ppm, respectively) than for the cis form, for which they are more shielded by the adjacent CH_3 groups (τ 8.86 and 8.95 ppm).

Completely similar ratios of the chemical shifts of the protons of the cis and trans forms and of their retention times were observed for 1,4,5-trimethyl-Δ^2-pyrazoline [1].

The stereoisomers of 4-methyl-5-ethyl-Δ^2-pyrazoline were identified by the same sort of comparison of the chromatograms and PMR spectra, and in this case the reaction mixture contained more trans form than cis form (3 : 2).

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