REASONS FOR THE FORMATION OF PYRAZOLINES OF ANOMALOUS STRUCTURE FROM UNSATURATED ALDEHYDES

B. V. Ioffe and V. V. Tsibul'skii

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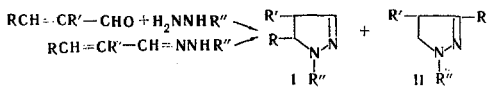
It is shown by gas-liquid chromatography and PMR spectroscopy that the reaction of alkylhydrazines with α-alkylacroleins, as distinct from the β-alkyl derivatives, results only in the formation of the normal products (1, 4-dialkyl-Δ^2-pyrazolines or the corresponding α-alkylacrolein alkylhydrazones). The latter isomerize on moderate heating with a catalytic amount of hydrochloric acid, the terminal C=C bond migrating to the middle of the chain to give α,β-dialkylacrolein or trialkylacrolein hydrazones rather than the expected cyclization products, 1, 4-dialkyl-Δ^2-pyrazolines. Condensation of isopropylhydrazine with α-methyl-β-ethylacrolein and cyclization of α-methyl-β-ethylacrolein isopropylhydrazone under forcing conditions gave the pyrazoline of anomalous structure, 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline, without any of the expected 1-isopropyl-4-methyl-5-ethyl-Δ^2-pyrazoline. The opinion is expressed that the formation of the pyrazoline with the anomalous structure is due to addition of the NH group of the hydrazine to the carbonyl group of the unsaturated aldehyde, which is sterically more accessible to the NH group than is the β-substituted C=C bond.

We have observed the formation of pyrazolines of anomalous structure in the cyclization of monoalkylhydrazones of unsaturated aldehydes [1, 2, 3], or directly, during the reaction of substituted acroleins with alkylhydrazines [1, 4]. The reaction of methyl, isobutyl, and especially isopropylhydrazine with crotonaldehyde [4] and cyclization of α,β-dimethylacrolein methyl- and isopropylhydrazones [1, 3] and of crotonaldehyde isopropylhydrazone [2] result in the formation of not only the normal reaction products (I), the structure of whose carbon skeleton corresponds to that of the starting aldehyde or hydrazone, but also of the anomalous compounds (II).



The formation of the latter could be due to an unknown rearrangement of the N-alkyl-Δ^2-pyrazolines themselves (N-unsubstituted pyrazolines undergo isomerization with migration of the C=N double bond and the proton [5, 6]). However, when 1, 5-dimethyl-, 1-isopropyl-5-methyl-, and 1-isopropyl-4-ethyl-Δ^2-pyrazoline were boiled with a few drops of concentrated hydrochloric acid (conditions used to cyclize unsaturated monoalkylhydrazones), we did not observe the formation of the isomeric pyrazolines, even in trace amounts. It must therefore be assumed, both on the basis of these results and on literature information [5], that N-alkyl-Δ^2-pyrazolines are stable and do not undergo isomerization. As has already been shown [4], the presence of a branched alkyl radical in the hydrazine and a β substituent in the α,β-unsaturated carbonyl compound results in the formation of the pyrazole with the anomalous structure by direct reaction of the hydrazine with the unsaturated aldehyde.

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It would be interesting to ascertain the effect on the formation of the pyrazoline ring of substituents in the α position of the unsaturated aldehyde. With this object in view, we condensed α-alkylacroleins with methyl- and isopropylhydrazine. Slow addition of the unsaturated aldehyde to the alkylhydrazine with ice-cooling afforded the pure 1-methyl-4-propyl- and 1-isopropyl-4-ethyl-Δ^2-pyrazolines (see Table 1), together with a mixture of α-isopropylacrolein isopropylhydrazone and 1, 4-diisopropyl-Δ^2-pyrazoline. If, however, the reaction of isopropylhydrazine with α-ethyl- [8], α-propyl-, and α-isopropylacrolein is carried out in weakly acid phosphate solution, the hydrazone is formed in every case (see Table 1). This has important practical implications, since the isopropylhydrazones of α-ethyl- and α-isopropylacrolein have nearly the same bp's as the corresponding 1, 4-dialkylpyrazolines, and it is not possible to separate them by fractional distillation; but by carrying out the reaction in weakly acid media, the pure unsaturated hydrazone could be isolated. Thus, substituents in the α position of the carbonyl compound do not hinder the formation of the pyrazoline ring with the expected structure.

On heating α-alkylacrolein isopropylhydrazones with a few drops of concentrated HCl, two reactions may occur: isomerization, as in the case of α-alkylacrolein dialkylhydrazones, accompanied by migration of the terminal double bond to the middle of the carbon chain [7], or the normal cyclization to 1, 4-dialkyl-Δ^2-pyrazolines. In fact, the reaction follows the first course, and when α-propyl- and α-isopropylacrolein isopropylhydrazones were heated at 100° for 10 h with the addition of a few drops of concentrated HCl, α-methyl-β-ethylacrolein and trimethylacrolein isopropylhydrazones were obtained in 40 and 57% yields, respectively. The structures of these compounds were proved by their PMR spectra and, in the first case, by comparison of its constants and PMR spectrum with those of an authentic sample, obtained from isopropylhydrazine and α-methyl-β-ethylacrolein [8].

It may, perhaps, be concluded on the basis of these results that the formation of N-alkylhydrazones and 1, 4-dialkylpyrazolines occurs concurrently, rather than consecutively, since otherwise α-alkylacrolein alkylhydrazones would have to cyclize readily to 1, 4-dialkyl-Δ^2-pyrazolines, which is not the case in practice.

The α-methyl-β-ethylacrolein isopropylhydrazones obtained by isomerization undergo cyclization only under very severe conditions. When they were heated with traces of concentrated HCL or with a catalytic amount of isopropylhydrazine hydrochloride (at 180-200°), there was obtained in poor yield (18%) the anomalous cyclization product, 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline (II), together with decomposition products and tars. None of the expected 1- isopropyl-4-methyl-5-ethyl-Δ^2-pyrazoline (I) was obtained. The pyrazoline II had the same retention time on three columns as an authentic sample, obtained from isopropylhydrazine and ethyl isopropenyl ketone.

It should be stressed that the expected pyrazoline (structure I) is not formed from α-methyl-β-ethylacrolein and isopropylhydrazine either, there being isolated from the pyrazoline fraction by preparative gas-liquid chromatography 12% of 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline (II), the structure of which was proved by comparison of its properties and retention times with those of an authentic sample, and also by the identity of their IR and PMR spectra. Therefore, the factors leading to the formation of the anomalous pyrazolines are the presence of the β substituent in the α,β-unsaturated aldehyde and branching of the alkyl radical in the hydrazine. The pyrazolines I are not formed, apparently, because of the strong steric effects of the isopropyl and ethyl groups in the 1 and 5 positions of the pyrazoline ring, as is indicated by examination of Stewart-Briegleb models.

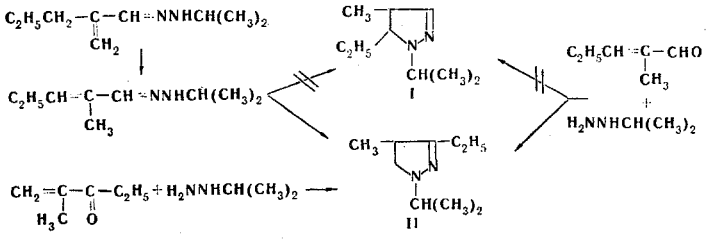
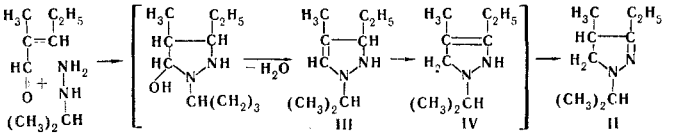


TABLE 1. Physicochemical Properties of Δ^2-Pyrazolines and Unsaturated Hydrazones

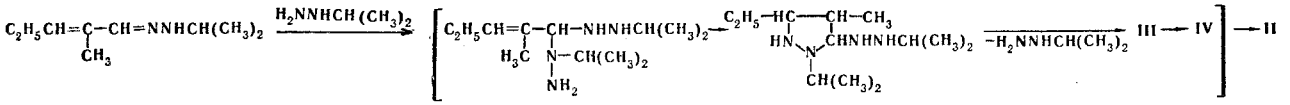
Compound	bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	n_C^{20}	Δ_{FC}	ω_{FCD}	MR_D		N, %		Molecular formula	Yield, %
							Found	Calculated	Found	Calculated		
1-Methyl-4-propylpyrazoline	54,0 (9)	0,8765	1,4513	1,4482	107,2	23,84	38,77	38,83	22,11; 22,14	22,20	$C_7H_{14}N_2$	70
1-Isopropyl-4-ethylpyrazoline	68 (10)	0,8685	1,4584	1,4552	115,6	25,21	43,97	43,48	20,19; 20,17	19,98	$C_8H_{16}N_2$	29
1-Isopropyl-3-ethyl-4-methylpyrazoline	69—71 (13)	0,8675	1,4547	1,4517	101,0	22,21	48,20	48,13	18,10; 18,14	18,16	$C_9H_{18}N_2$	22
1-Isopropyl-3-ethyl-4-methylpyrazoline, from isopropylhydrazine and α-methyl-β-ethylacrolein *	63,5 (9)	0,8699	1,4561	1,4521	117,2	25,70	48,12	48,13	18,06; 18,24	18,16	$C_9H_{18}N_2$	—
α-Propylacrolein isopropylhydrazone	76,0—76,8 (9)	0,8424	1,4815	1,4765	—	—	52,12	49,58	18,04; 17,95	18,16	$C_9H_{18}N_2$	58
α-Isopropylacrolein isopropylhydrazone	72,0—72,4 (8)	0,8393	1,4803	1,4754	184,1	38,33	52,24	49,58	18,05; 18,12	18,16	$C_9H_{18}N_2$	38
Trimethylacrolein isopropylhydrazone	91—92 (8)	0,8662	1,5068	1,5008	223,8	44,16	53,01	49,58	17,97; 18,11	18,16	$C_9H_{18}N_2$	57

* Obtained chromatographically pure, by preparative gas chromatography.

It is most likely that steric hindrance of the addition of the NH group to the β-substituted C=C bond results in reaction of the NH with the sterically more accessible carbonyl group, the NH_2 group adding to the C=C bond. The reason for the formation of the anomalous pyrazoline II appears to be, not a skeletal rearrangement, but a different mode of addition of the alkylhydrazine to the α, β-unsaturated carbonyl compound. The dehydration of the initially formed hydroxypyrazoline and the migration of the double bond may be represented by the scheme



The anomalous cyclization of the alkylhydrazones of unsaturated aldehydes under the catalytic influence of alkylhydrazine salts may be considered to be a consequence of the addition of the NH group of the alkylhydrazine to the C=N bond, followed by cyclization.



EXPERIMENTAL

Reaction of Methylhydrazine with α-Propylacrolein. α-Propylacrolein [24.5 g (0.25 mole)] was added carefully with stirring and ice-salt cooling to 11.5 g (0.25 mole) of methylhydrazine [7]. After removal of water, and drying over potassium carbonate, there was obtained 31.2 g of a mixture, which on vacuum distillation through a column afforded 21.7 g (70%) of 1-methyl-4-propyl-Δ^2-pyrazoline (98.5% pure by GLC), with the constants given in the table. IR spectrum: strong band at 1576 cm^{-1}, characteristic of C=N bond in 3-unsubstituted pyrazolines [10], and at 3054 cm^{-1} (H–C=).

Reaction of Isopropylhydrazine with α-Ethylacrolein. Similarly, from 37 g (0.5 mole) of isopropylhydrazine and 42 g (0.5 mole) of α-ethylacrolein [8] there was obtained 65.8 g of a mixture of products (n_D^{20} 1.4780). Distillation gave 20.4 g (29%) of 1-isopropyl-4-ethyl-Δ^2-pyrazoline (see Table 1). It was 95.8% pure by GLC. Further distillation in vacuo (10 mm) of the residual dark red oil (40 g) did not afford any more volatile material. IR spectrum: 3053 cm^{-1} (H–C=), and 1582 cm^{-1} (C=N [10]). PMR spectrum: $CH_3-C-C_{(4)}-$, triplet with τ 9.04 ppm (J 5.5 Hz); $(CH_3)_2C-$, doublet with τ 8.81 ppm (J 6.5 Hz); H–C = N–, singlet with τ 3.50 ppm; ring protons and $C-CH_2-C_{(4)}$, multiplet at 6.8-7.4 ppm.

Reaction of Isopropylhydrazine with α-Methyl-β-ethylacrolein. Obtained as above, from 37 g (0.5 mole) of isopropylhydrazine and 49 g (0.5 mole) of α-methyl-β-ethylacrolein, was 71.9 g of organic layer (n_D^{20} 1.4820), distillation of which at 9 mm afforded the following fractions: 1) 28-64°; n_D^{20} 1.4480 (6.2 g) 2) 64-70°; n_D^{20} 1.4596 (9.5 g) 3) 70-84°; n_D^{20} 1.4723 (3.9 g) (intermediate) 4) 84-85.5°; n_D^{20} 1.4950 (45.8 g). The residue was 2.2 g of brown oil, n_D^{20} 1.4848. Chromatography showed fraction 2 to contain 91% of the main component, which was obtained in a chromatographically pure state by preparative gas chromatography on a column containing 25% of thermostable silicone resin with ethyl groups (TSRE) on Spherochrome-1 (TNDM, 0.3-0.5 mm fraction (see table). This was shown to be identical with authentic 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline, obtained from ethyl isopropenyl ketone and isopropylhydrazine, on three different columns [15% mixture of polyethylene glycol-4000 and triethanolamine (1:1) on Spherochrome-1 (0.3-0.5 mm); 25% polyethylene glycol adipate and triethanolamine (1:1) on Spherochrome-1 (0.3-0.5 mm); and 15% TSRE on Spherochrome-1 (0.3-0.5 mm). Column length 1 and 1.2 m]. The constants, IR, and PMR spectra were completely identical with the spectra of authentic 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline. The overall yield of the pyrazoline in fraction 2 amounted to 12%. Repeated distillation of fractions 3 and 4 gave a 60% yield of α-methyl-β-ethylacrolein isopropylhydrazone, whose constants were identical with those reported previously [8] (the reaction of isopropylhydrazine with α-methyl-β-ethylacrolein was carried out in weakly acid phosphate medium, and no pyrazoline was found in the reaction products).

1-Isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline (84% compound) was obtained from 11.5 g (0.155 mole) of isopropylhydrazine and 15.2 g of ethyl isopropenyl ketone [11] (see Table 1). The frequency $\nu_{C=N}$ 1612 cm^{-1} in the IR spectrum corresponded to the presence of a substituent in the 3 position [10], which is also confirmed by the absence in the PMR spectrum of signals with $\tau < 6$ ppm.

Reaction of isopropylhydrazine with α-propylacrolein was carried out similarly but with the addition of sodium dihydrogen phosphate. To a mixture of 37 g (0.5 mole) of isopropylhydrazine and 78 g of $NaH_2PO_4 \cdot 2H_2O$ in 150 ml of water was added over 10 min with vigorous stirring (emulsion) 49 g (0.5 mole) of α-propylacrolein [7]. The mixture was then heated to 80° for a further 2 h, and the organic layer was separated and dried over potassium carbonate (66 g, n_D^{20} 1.4780). Distillation afforded 43.3 g (58%) of α-propylacrolein isopropylhydrazone (see table), IR spectrum, cm^{-1}; 1579 and 1617 (C=C–C=N) [12], 3082 ($H_2C=$), and 3236 (N–H).

Reaction of isopropylhydrazine with α-isopropylacrolein was carried out as described above. From 37 g (0.5 mole) of isopropylhydrazine, 78 g of $NaH_2PO_4 \cdot 2H_2O$ and 49 g of isopropylacrolein [7], there was obtained after two vacuum distillations 29.7 g (38%) of α-isopropylacrolein isopropylhydrazone (see table). IR spectrum, cm^{-1}: 1578 and 1614 (C=C–C=N [12]), 3090 ($H_2C=$), and 3235 (N–H). Repeated fractionation of the volatile fractions gave 5.2 g of a mixture, bp 70.5-70.8° (8 mm); n_D^{20} 1.4712, containing 55% of α-isopropylacrolein isopropylhydrazone and 45% of 1,4-diisopropyl-Δ^2-pyrazoline, by GLC. A quantitative analysis of the H–C=N signals in the PMR spectrum at τ 3.47 and 2.78 ppm (for the pyrazoline and the hydrazone, respectively [13]) gave a similar isomer ratio (43 and 57%).

Isomerization of α-Propylacrolein Isopropylhydrazone. In a flask fitted with a reflux condenser was heated at 100° for 10 h a mixture of 25 g of α-propylacrolein isopropylhydrazone and 0.5 g of isopropylhydrazine hydrochloride. Vacuum distillation of the reaction mixture afforded 10 g (40%) of α-methyl-β-ethylacrolein isopropylhydrazone, bp 93.3-93.7° (9 mm): d_4^{20} 0.8521; n_D^{20} 1.4928; n_C^{20} 1.4874; Δ_{FC} 199.8; ω_{FCD} 40.54; MR_D 52.60 (calculated 49.58); EM_D 3.02 (cf [8]). After hydrolysis with 6 N sulfuric acid, there was obtained α-methyl-β-ethylacrolein 2,4-dinitrophenylhydrazone, mp 160-161° (undepressed on admixture with an authentic sample). PMR spectrum: $(CH_3)_2CH-$, doublet and septet with τ 8.98 and 6.59 ppm (J 6.5 Hz) respectively; $CH_3-C=$, singlet with τ 8.19 ppm; N–H–, singlet with τ 5.04 ppm; CH=C–, triplet with τ 4.56 ppm (J 7.0 Hz), H–C=N–, two singlets with τ 2.76 and 2.30 ppm for the trans (85%) and cis forms (15%) respectively [14], $CH_3-C-C=$, triplet, superimposed on the doublet due to the isopropyl group, $C-CH_2-C=$, multiplet with τ 7.4 ppm.

Conversion of α-Propylacrolein Isopropylhydrazone under Severe Conditions. After boiling 15 g of α-propylacrolein isopropylhydrazone with a few drops of concentrated HCl for 10 h, the following fractions were obtained: 1) 42-64° (9 mm); n_D^{20} 1.4482; 1.6 g (by GLC, this contains 41% of acetone isopropylhydrazone and 34% of 1-isopropyl-3-ethyl-4-methyl-Δ^2-pyrazoline (II): 2) 64-71° (9 mm); n_D^{20} 1.4548; 3.1 g (6% of acetone isopropylhydrazone and 67% of II) (the overall yield of II from both fractions was 18%): 3) 71-85° (9 mm); n_D^{20} 1.4620; 2.1 g (not chromatographed), and 5 g of residual oil.

Conversion of α-methyl-β-ethylacrolein isopropylhydrazone by isopropylhydrazine hydrochloride under similar conditions proceeded similarly.

Isomerization of α-Isopropylacrolein Isopropylhydrazone. Under the conditions employed for the isomerization of α-propylacrolein isopropylhydrazone, 27 g of α-isopropylacrolein isopropylhydrazone afforded 15.1 g (57%) of trimethylacrolein isopropylhydrazone (see Table 1). The trimethylacrolein 2,4-dinitrophenylhydrazone obtained after hydrolysis with dilute (1:6) sulfuric acid had mp 194.5-195.5° (198° [15]). IR spectrum, cm^{-1}: 1565 and 1634 (C=C–C=N [12]); 3234 (N–H). PMR spectrum $(CH_3)_2CH-$, doublet and septet with τ 8.91 and 6.59 ppm (J 7.0 Hz) respectively; $(CH_3)_2C=C(CH_3)-$, strong singlet due to the three methyl groups with τ 8.21 ppm: N–H–, singlet with τ 4.96 ppm; H–C=N–, singlet with τ 2.23 ppm.

Attempts to Isomerize N-Alkyl-Δ^2-pyrazolines. In a flask fitted with a reflux condenser was boiled for 3-4 h 3 g of the pyrazoline (1,5-dimethyl- [4], 1-isopropyl-5-methyl- [16], or 1-isopropyl-4-ethylpyrazoline). No other isomers were found when the mixtures were chromatographed under the conditions previously used [4].

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