REARRANGEMENTS IN THE FORMATION OF PYRAZOLINES FROM ALKYL HYDRAZINES AND UNSATURATED CARBONYL COMPOUNDS

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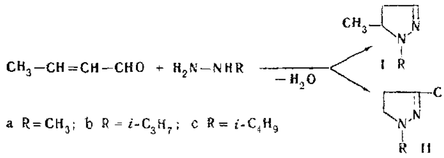
The isomeric composition of the 2-pyrazolines obtained by the condensation of croton aldehyde and methyl vinyl ketone with C_1-C_4 monoalkyl hydrazines has been studied by the GLC method. It has been shown that in the reaction of croton aldehyde with isopropyl hydrazine, isobutyl hydrazine, and, to a smaller extent, with methyl hydrazine, in addition to the 1-alkyl-5-methyl-2-pyrazolines the 1,3-isomers are formed. In other cases, only one pyrazoline, corresponding to the structure of the carbonyl compound, is formed. Eight previously-unknown dialkyl-2-pyrazolines are described.

Until very recently it was considered that the structure of the pyrazolines obtained by the condensation of hydrazines with unsaturated carbonyl compounds is determined unambiguously by the structure of the latter. The question of the possibility of the formation of isomers in the closure of the pyrazoline ring was not even posed, and the condensation products were ascribed the structure of the carbon skeleton of the initial carbonyl reactant without proof. However, in an NMR and GLC study of the products of the reaction of methyl hydrazine with tiglaldehyde it was established [1] that in addition to the two expected stereoisomeric 1, 4, 5-trimethyl-2 pyrazolines an appreciable amount of their structural isomer—1, 3, 4-trimethyl-2-pyrazoline was obtained. Furthermore, it has been shown [2] that in the cyclization of the isopropyl hydrazones of unsaturated aldehydes the main reaction product is a pyrazoline with a modified carbon skeleton, while the normal pyrazoline is either not formed at all (from α-ethylacrolein isopropylhydrazone) or is produced in very small amount (cyclization of croton aldehydeisopropyl hydrazone). These facts have induced us to return to a systematic study of the rearrangements accompanying the closure of the pyrazoline ring. It was necessary first of all to determine how widespread these rearrangements are and what features of the structure of the reactants favor them. For this purpose, the simplest unsaturated carbonyl compounds, croton aldehyde and methyl vinyl ketone, were condensed with methyl, ethyl, n-propyl, isopropyl, and isobutyl hydrazines under the usual conditions—with the slow addition of the carbonyl compound to the cooled alkyl hydrazine. The pyrazoline fraction obtained by vacuum distillation of the reaction mixture was studied by means of GLC and IR spectroscopy. It was found that in the majority of cases (in all the experiments with methyl vinyl ketone and also in the reaction of croton aldehyde with methyln-propyl, and n-butyl hydrazines) only one pyrazoline, the structure of which corresponded to the initial carbonyl compound, was obtained. However, in the condensation of methyl, isopropyl, and isobutyl hydrazines with croton aldehyde a mixture of two isomeric pyrazolines was obtained in each case. The second isomers were shown by GLC on stationary phases of different polarities to be identical with the products of the reaction of the same alkyl hydrazines and methyl vinyl ketone, i.e., with 1-alkyl-3-methyl-2-pyrazolines:



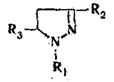
a $R=CH_3$; b $R=i\text{-}C_3H_7$; c $R=i\text{-}C_4H_9$

The formation in these cases of mixtures of pyrazolines with and without the substituent in position 3 was also confirmed by IR spectroscopy. In addition to the strong bands of the stretching vibrations in the C=N group unsubstituted in position 3 of the 2-pyrazolines at 1580 cm^{-1} [3], the IR spectra of the three substances obtained from croton aldehyde also had the bands characteristic for 3-alkyl-2-pyrazolines at 1620 cm^{-1} [3] (see Table 1), the relative intensities of which varied according to the areas of the peaks of the 1-alkyl-3-methyl-2-pyrazolines on the chromatograms. In the reaction of isobutyl hydrazine with croton aldehydes, the rearrangement product was isolated in the form of a solution in CCl_4 on a "Tsvet-3" chromatograph with a preparative attachment and was shown to be identical with the 1-isobutyl-3-methyl-2-pyrazoline from methyl vinyl ketone by the coincidence of the bands in the "fingerprint" region.

The contents of anomalous product II in the mixture with I amounted (according to GLC) to 34 and 16% in the reaction with isopropyl and isobutyl hydrazines, respectively, and only 1% in the case of methyl hydrazine. If this last case (with an extremely small amount of anomalous product) is disregarded, it is appropriate to mention that the change in the carbon skeleton in the formation of the pyrazolines takes place when the alkyl hydrazine has a secondary or branched radical and the double bond of the carbonyl compound is located in the center of the chain. It is precisely these two factors—the structure of the alkyl radical of the hydrazine and the position of the double bond—that were noted previously among the essential factors determining the possibility of the closure of pyrazoline rings in the reactions of unsaturated carbonyl compounds with alkyl- and dialkyl hydrazines [4–6]. When croton aldehyde was condensed with isopropyl hydrazine, the reaction mixture contained, in addition to pyrazolines, a considerable amount of the unsaturated hydrazone and, probably, its dimer, and in the reaction with isobutyl hydrazine high-boiling substances

Table 1

Individual Dialkyl-2-pyrazolines Obtained from Croton Aldehyde and Methyl Vinyl Ketone



R_1	R_2	R_3	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	n_C^{20}	Δ_{FC}^{20}	ω_{FCD}	MR_D		Molecular weight (cryoscopic)		Empirical formula	N, %		Purity	$\gamma_{C=N}$, cm^{-1}	Yield, %
									found	calculated	found	calculated		found	calculated			
C_2H_5	H	CH_3	60.6—60.8 (50)*	0.8876	1.4505	1.4473	112.4	24.95	34.00	34.19	110.4: 113.7	112.2	$C_6H_{12}N_2$	25.12: 25.07	24.98	Chrp	1580	43
C_2H_5	CH_3	H	65.8—66.0 (51)	0.8915	1.4551	1.4519	114.8	25.23	34.15	34.19	108.7; 106.4	112.2	$C_6H_{12}N_2$	25.13; 25.17	24.98	Chrp	1625	42
n-C_3H_7	H	CH_3	61.5—62.0 (25)	0.8772	1.4514	1.4484	108.3	23.99	38.78	38.83	126.4; 124.8	126.2	$C_7H_{14}N_2$	22.18; 22.31	22.20	99.6%	1577	38
n-C_3H_7	CH_3	H	64.0 (16)	0.8830	1.4572	1.4541	110.7	24.21	38.84	38.83	125.3; 123.8	126.2	$C_7H_{14}N_2$	22.21; 22.38	22.20	95.5%	1623	64
i-C_3H_7	CH_3	H	61.2—61.4 (25)	0.8807	1.4574	1.4542	113.5	24.82	39.11	38.83	125.7; 129.0	126.2	$C_7H_{14}N_2$	22.00; 22.54	22.20	Chrp.	1625	50
n-C_4H_9	H	CH_3	79.0—79.8 (25)	0.8734	1.4534	1.4504	107.0	23.60	43.42	43.48	139.2; 138.7	140.2	$C_8H_{16}N_2$	20.10; 19.97	19.98	98.2%	1580	58
i-C_4H_9	H	CH_3	69.5—71.5 (25)*	0.8649	1.4480	1.4450	105.6	23.57	43.40	43.48	142.0; 137.5	140.2	$C_8H_{16}N_2$	19.80; 19.71	19.98	Chrp	1580	41
i-C_4H_9	CH_3	H	72.5—73.0 (22)	0.8658	1.4538	1.4508	107.8	23.75	43.84	43.48	138.7; 135.4	140.2	$C_8H_{16}N_2$	19.89; 19.77	19.98	98.6%	1623	50

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*Bp and yield of the substance before purification by gas-liquid chromatography.

Table 2

Ratios of the Retention Times of the 1-Alkyl-3-methyl-2-pyrazolines to Those of the 1-Alkyl-5-methyl Isomers

Alkyl	Stationary liquid phase		
	Cyanoethylated mannitol (10%)	Triethanolamine + polyethylene glycol, 1:1 (15%)	Apiezon L (10%)
Methyl	1.57	1.60	1.63
Ethyl	1.84	1.65	1.41
n-Propyl	1.62	1.75	1.42
Isopropyl	1.45	1.58	1.39
Isobutyl	1.47	1.59	1.41

which underwent conversion into pyrazolines on distillation were again obtained. Thus, the impression is created that the formation of the isomeric pyrazolines is connected in some way with the sterio conditions of the closure of the ring. As a preliminary working hypothesis one may adopt the assumption that the formation of the pyrazolines is accompanied by rearrangements in those cases in which there is hindrance to cyclization by addition to the C=C double bond.

EXPERIMENTAL

The alkyl hydrazines were prepared by the alkylation of hydrazine hydrate by the method of Kost and Sagitullin [7], with some improvements [8]. Yields and constants corresponded to those given previously [8]. The croton aldehyde and methyl vinyl ketone were commercial materials additionally distilled through a column and free from isomers (according to GLC).

Synthesis of 2-pyrazoline from alkyl hydrazines and α, β-unsaturated carbonyl compounds.* With ice-salt cooling and stirring, an equimolar amount of unsaturated carbonyl compound was added dropwise to an alkyl hydrazine (0.1–0.5 mole). The temperature of the reaction mixture was kept between −10 and +20° C. After the end of the addition, the reaction mixture was stirred at room temperature for another 1–2 hr and the products were salted out, dried with potassium carbonate for a day, and distilled in vacuum through a Vigreux column (12 theoretical plates) in a current of nitrogen.

The main fraction, collected in a range of about 1° C with a yield of 38–64%, was subjected to chromatographic analysis. To obtain more accurate constants, samples of 1-ethyl-5-methyl- and 1-isobutyl-5-methyl-2-pyrazolines were purified additionally by preparative gas chromatography. The characteristics of all the individual pyrazolines obtained for the first time are given in Table 1.

Reaction of isopropyl hydrazine with croton aldehyde. Under the conditions described above, 74 g (1 mole) of isopropyl hydrazine and 70 g (1 mole) of croton aldehyde yielded, after drying, 124 g of organic layer (n_D^{20} 1.4870). Vacuum distillation at 26 mm furnished the following fraction: 1) 37–55.5° C; n_D^{20} 1.4390; 6.3 g (84% of **Ib**, 3.4% of **IIb**); 2) 55.5–64.5° C; n_D^{20} 1.4520; 21.2g (58.4% of of **Ib**, 33.7% of **IIb** and 2.8% of 1-isopropyl-3-methylpyrazole; the total yield of pyrazolines was 17% of theoretical); 3) 64.5–83.0° C; n_D^{20} 1.4660; 6.0 g, an intermediate fraction; 4) 83.0–83.5° C; n_D^{20} 1.4936; 20.3 g (16.2%), croton aldehyde isopropyl hydrazone. The residue amounted to 62.4 g. The compositions of the fractions were determined by gas-chromatographic analysis. A more complete proof of the structure of the pyrazolines **Ib** and **IIb** by chemical methods has been given previously [2] for fractions of similar composition.

The redistillation of fractions 3 and 4 yielded croton aldehyde isopropyl hydrazone with bp 85.5–86.2° C (27 mm); d_4^{20} 0.8519; n_4^{20} 1.0516; n_4^{20} 1.4954, Δ_{FC} 204.45; ω_{FCD} 40.77. Found, %: N 22.11, 21.81; mol. wt. 129.6, 128.5; MR_D 43.45; EM_D 3.23. Calculated for $C_7H_{14}N_2$, %: 22.20; mol. wt. 126.3; MR_D 40.22. IR spectrum, cm^{-1}: 1655 and 1581 (C=C—C=N), 3236 (N—H) and 3031 (H—C=). The substance was unstable and was readily converted into a pyrazoline on distillation [2].

The residue was distilled separately, giving 37.8 (30%) of a fairly viscous liquid with bp 125–128° C (3 mm); d_4^{20} 0.9573; n_D^{20} 1.5079; MR_D 78.66; mol. wt. 255.9; 244.8. Calculated for $C_{14}H_{28}N_4$, %: MR_D 78.25 (one C=C and one C=N bond); mol. wt. 252.6. The substance reduced Fehling's solution on heating with cuprous oxide (like hydrazones). IR spectrum, cm^{-1}: 3420 (N—H), 1678 (C=C), and 1625 (C=N). The product is apparently a mixture of cyclic dimers of croton aldehyde isopropyl hydrazone similar to those formed in the reaction with methacrolein [9].

Reaction of isobutyl hydrazine with croton aldehyde. Under the same conditions, 220 g (0.25 mole) of isobutyl hydrazine and 17.5 g (0.25 mole) of croton aldehyde gave 34.8 g of an organic layer (n_D^{20} 1.4734). The following fractions were isolated in a vacuum of 25 mm: 1) 65–69.5°; n_D^{20} 1.4440; 1.0 g (93% I_C); 2) 69.5–71.5°; n_D^{20} 1.4474; 14.2 g (41%; mixture of 84.2% of **IC** and 15.8% of **IIC**); 3) 71.5–97°; n_D^{20} 1.4545; 4.0 g (5.6% of **IC**, 78.3% of **IIC**); 4) 97–110°; n_D^{20} 1.4962; 8.3 g. The residue consisted of 4.3 g of a resin.

By preparative chromatography, chromatographically pure **Ic** (Table 1) and a solution of **IIc** in CCl_4 were isolated from fraction 2. The high-boiling fraction 4 was readily converted on distillation or chromatography into a mixture of the pyrazolines **Ic** and **IIc**, and darkened very rapidly on standing.

Gas-liquid chromatography. The pyrazolines described in the present paper are fairly stable compounds and can be subjected to chromatographic analysis not only in glass but in steel columns at temperatures of up to 130° C. However, when high-boiling fractions were isolated from the product of the reaction of alkyl hydrazines with unsaturated carbonyl compounds, the chromatographic analysis of these fractions or of the reaction mixtures themselves could not be used since they were tenaciously retained in the column, underwent decomposition, and were converted into pyrazolines during chromatography. It was impossible to obtain reproducible chromatograms for such substances even in glass columns and with the complete exclusion of contact with metal surfaces and the introduction of the sample directly into the column with a glass capillary [10].

The analysis of the pyrazolines was carried out on "Tsvet-1" and "Tsvet-3" chromatographs fitted with glass or metal columns, as described previously. In all cases the low-boiling 1-alkyl-5-methyl-2-pyrazolines had shorter retention times than the 1-alkyl-3-methyl-2-pyrazolines isomeric with them (see Table 2).

Preparative separation was carried out in an attachment to the "Tsvet-3" chromatograph. The purification of the 1-ethyl-5-methyl-2-pyrazoline was carried out in a meter steel column with aidiameter of 15 mm containing 15% of a mixture of treithanolamine and polyethylene glycol-4000 (1:1) on TND-TS-M (0.3–0.5 mm), and the separation of 1-isobutyl-3-methyl- and 1-isobutyl-5-methyl-2-pyrazolines was carried out on a meter column containing 25% of poly(ethylene glycol adipate) on the same support. Nitrogen was used as the carrier gas (at a rate of 300–500 ml/min). The substances isolated after preparative chromatography in amounts of up to 5 g were

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*The synthesis of 1-n-butyl-5-methyl-2-pyrazoline and of 1-isopropyl-3-methyl-2-pyrazoline was performed by graduate students N. B. Burmanova and E. A. Zagradina.

subsequently distilled in order to free them from traces of the stationary liquid phase.

REFERENCES

1. B. V. Ioffe, V. V. Tsibul'skii, V. S. Stopskii, and Z. I. Sergeeva, KhGS [Chemistry of Heterocyclic Compounds], **2**, 932, 1966.
2. B. V. Ioffe and V. V. Tsibul'skii, ZhOrKh, **3**, 1903, 1967; 1968.
3. B. V. Ioffe, KhGS [Chemistry of Heterocyclic Compounds], **4**, 1089, 1968.
4. B. V. Ioffe and K. N. Zelenin, ZhOKh, 33, 3589, 1963.
5. B. V. Ioffe and E. I. Sabinina, ZhOKh, **33**, 2188. 1963.
6. N. L. Zelenina and B. V. Ioffe, Abstracts of Reports to the Second All-Union Conference on the Chemistry of Nitrogen-Containing Heterocycles [in Russian], Rostov-on-Don, 1966.
7. A. N. Kost and R. S. Sagitullin, USSR patent no. 126117, 1959; ZhOKh, **33**, 867, 1963.
8. B. V. Ioffe, V. S. Stopskii, and Z. I. Sergeeva, ZhOrKh, **4**, 906, 1968.
9. B. V. Ioffe, Z. I. Sergeeva, V. V. Tsibul'skii, and N. I. Klyueva, ZhOrKh, **3**, 988, 1967.
10. A. G. Vitenberg, Yu. V. Priporov, and V. V. Tsibul'skii, Zav. lab., **34**, 156, 1968.

9 February 1968 Leningrad State University