SYNTHESIS OF PYRAZOLINES BY THE CONDENSATION OF MONOALKYL HYDRAZONES WITH ALDEHYDES*

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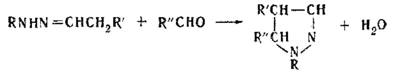
Acetaldehyde readily condenses with its monalkyl hydrazones with the formation of 1-alkyl-5-methyl-2-pyrazolines. A number of pure 2-pyrazolines have been synthesized in this way with yields of 40–60%. In the condensation of propionaldehyde with its isopropyl hydrazone, because of the occurrence of rearrangements and the nonstereospecificity of the process, a mixture of structural and stereoisomeric 2-pyrazolines is formed. The promising condensation of aldehydes with monalkyl hydrazones of other aldehydes and ketones is accompanied by "transhydrazonation," which limits the preparative possibilities of this reaction.

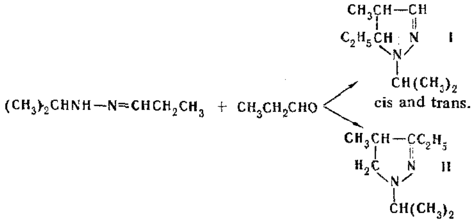
In the preparation of alkyl hydrazones of aliphatic aldehydes, it has been observed [1] that, in addition to the normal condensation products, pyrazolines are formed. Thus, the reaction of ethyl hydrazine and acetaldehyde gave a 31% yield of 1-ethyl-5-methyl-2-pyrazoline. It was natural to assume that the pyrazolines are the products of a secondary condensation of the hydrazone formed with the aldehyde. Until recently, such reactions were unknown in the hydrazone series, although their closest analogs, aldimines, react with one another with the formation of aminoimines and the subsequent splitting out of an amine [2], and also with carbonyl [3] and other compounds having an active methylene group in the manner of an aldol condensation [4]. In the concluding stage of the present work, a paper was published on the synthesis of pyrazolines from methyl hydrazine and aldehydes [5], the authors of which likewise considered the pyrazolines as products of the interaction of the initially-formed hydrazones with an excess of the aldehydes and confirmed this assumption by obtaining 5-hexyl-1-methyl-4-pentyl-2-pyrazoline from heptanal methyl hydrazone and heptanal.

The possibility of the condensation of monalkyl hydrazones with aldehydes is of undoubted theoretical interest, and its practical importance could lie in the synthesis of pyrazolines difficultly accessible because of the limitations inherent in the method of condensing hydrazines with a, β-unsaturated carbonyl compounds [6] or because of the difficulty of obtaining the initial unsaturated compound. The special investigation that we have undertaken in this connection has shown that aldehyde monoalkyl hydrazones generally react with aldehydes with a spontaneous rise in temperature to 50–60° C and the formation of pyrazolines:



The condensation of acetaldehyde with its ethyl, n-propyl, n-butyl, and isopropyl hydrazones yielded the corresponding 1-alkyl-5-methyl-2-pyrazolines with yields of of the order of 40–60% (see table). Unlike hydrazines with primary radicals, acetaldehyde isopropyl hydrazone reacted far less readily: it was necessary to boil the reaction mixture with an excess of the aldehyde in order to obtain 1-isopropyl-5-methyl-2-pyrazoline with a yield of 49%. It is interesting to note that, according to GLC, this product was not contaminated with 1-isopropyl-3-methyl-2-pyrazoline, while the condensation of isopropyl hydrazine with crotonaldehyde forms a mixture of isomers [7].

The condensation of propionaldehyde with its isopropyl hydrazone requires still more severe conditions. Only after prolonged boiling of the reaction mixture was it possible to obtain a pyrazoline fraction which, however, contained, in addition to the expected 5-ethyl-1-isopropyl-4-methyl-2-pyrazoline (I) its structural isomer—3-ethyl-1-isopropyl-4-methyl-2-pyrazoline (II), which was shown by the GLC method to be identical with the substance obtained from isopropyl hydrazine and isopropenyl methyl ketone [7].



Composition of the 1-Alkyl-5-methyl-2-pyrazolines Obtained by the Condensation of Acetaldehyde with its Monoalkyl Hydrazones

Compound	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Yield, %
				found	calculated	
1-Ethyl-5-methyl-2-pyrazoline	32.0—32.6 (10)	0.8785	1.4504	34.31	34.18	39
1-n-Propyl-5-methyl-2-pyrazoline	57.5—57.9 (50)	0.8764	1.4512	38.73	38.83	59
1-n-Butyl-5-methyl-2-pyrazoline	78.9—79.8 (25)	0.8731	1.4532	43.43	43.48	40
1-Isopropyl-5-methyl-2-pyrazoline	51.0—51.7 (26)	0.8826	1.4518	38.50	38.60	49

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*From the text of the thesis of N. B. Burmanova, defended in May, 1967.

Thus, in the condensation of propionaldehyde isopropyl hydrazone with propionaldehyde a partial (50%) rearrangement apparently takes place. On the basis of the PMR spectrum (Fig. 1), showing the absence from the reaction products of all the structurally isomeric 2-pyrazolines $C_9H_{18}N_2$ apart from 3-(or 5-)ethyl-1-isopropyl-4-methyl-2-pyrazoline (absence of HN signals with τ 4.1–4.2 ppm, $CH_3NCH_3C^3$ and CH_3C^5 at 7.3, 8.2, and 8.8 ppm, respectively, and the presence of two HC^3 signals τ 3.55 and 3.78 ppm), it can be stated that both stereoisomers of I are formed. The PMR spectrum of the 5-ethyl-1,4-dimethyl-2-pyrazoline obtained from methyl hydrazine and propionaldehyde [5] also contained two HC^3 signals, which were erroneously interpreted by Rabjohn et al. [5] as a doublet with J = 14 Hz (the value of J_{HC_3} in the 2-pyrazolines does not exceed 2 Hz [8]). The simultaneous formation of the cis and trans isomers in almost equal amounts shows the nonstereospecificity of the condensation of aldehyde monoalkyl hydrazones with aldehydes.

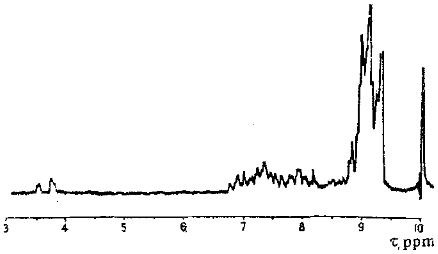
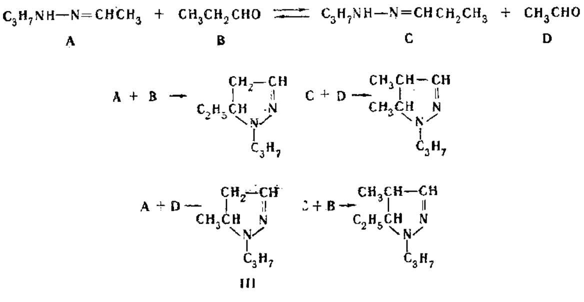


Fig. 1. PMR spectrum of the mixture of pyrazolines obtained from propionaldehyde and its isopropyl hydrazone.

It appeared of interest to carry out the condensation of an aldehyde with a monoalkyl hydrazone of a different aldehyde, which would enable the radicals in position 4 and 5 of the pyrazoline synthesized to be varied. When propionaldehyde n-propyl hydrazone was condensed with acetaldehyde and when acetaldehyde n-propyl hydrazone was condensed with propionaldehyde, mixtures of four 2-pyrazolines of identical compositions were obtained (Fig. 2, a and b). This result may be considered as the consequence of the displacement of the aldehyde residue of the hydrazones by the other aldehyde, i.e., of the "transhydrazonation" of the aldehyde.

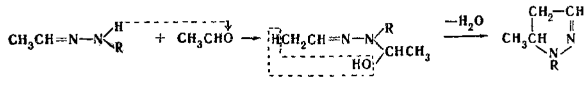


$$\underset{A}{C_3H_7NH{-}N{=}CHCH_3} + \underset{B}{CH_3CH_2CHO} \rightleftharpoons \underset{C}{C_3H_7NH{-}N{=}CHCH_2CH_3} + \underset{D}{CH_3CHO}$$

It must be mentioned that in both cases the main product was the pyrazoline III. The rate of condensation of acetaldehyde with its n-propyl hydrazone (A + D) is apparently the highest. These results are in agreement with a statement [5] on the formation of a mixture of four pyrazolines in the condensation of n-butyraldehyde with heptanol methyl hydrazone also made on the basis of a chromatographic analysis of the reaction mixture.

Acetone n-propyl hydrazone and acetaldehyde yielded only 5-methyl-1-n-propyl-2-pyrazoline, the product of the condensation of acetaldehyde with its n-propyl hydrazone (Fig. 2c). The formation of only this one pyrazoline shows that the displacement of the ketone from its hydrazone by the aldehyde takes place readily, and the rate of condensation of acetaldehyde and its alkyl hydrazone is in any case far greater than the rate of condensation with an acetone monoalkyl hydrazone and of the condensation of acetone with the hydrazones.

The available experimental results did not permit an unambiguous decision concerning the mechanism of the condensation of hydrazones with aldehydes. The assumption [5] that the reaction takes place in a similar manner to the formation of aldehyde ammonias with the subsequent splitting out of water



is not the only possible one. The pyrazoline may also be formed as the result of the reaction of the hydrazone with the aldehyde or of two hydrazones in the manner of an aldol condensation. However, attempts to affect the self-condensation of acetaldehyde n-butyl hydrazone under the action of alkali, and the condensation of acetaldehyde with its dimethyl hydrazone (having no NH group) gave a negative result. Thus, a scheme including in the first stage the addition of the NH group to the carbonyl with the subsequent splitting out of water from the "semihydrazinal" hydroxyl and the β-hydrogen of the alkylidene radical of the hydrazone may be regarded as the most likely.

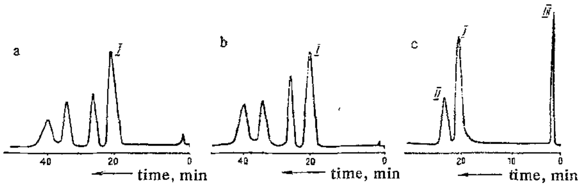


Fig. 2. Chromatograms of reaction mixtures obtained by the condensation of: a) propionaldehyde n-propyl hydrazone with acetaldehyde; b) acetaldehyde n-propyl hydrazone with propionaldehyde; c) acetone n-propyl hydrazone with acetaldehyde (I is 5-methyl-1-n-propyl-2-pyrazoline, II is acetone n-propyl hydrazone, III is acetone).

EXPERIMENTAL

The initial alkyl hydrazones were synthesized from monalkyl hydrazines and carbonyl compounds as described previously [1].

Condensation of acetaldehyde with monalkyl hydrazines. With vigorous stirring, 1.2 mole of acetaldehyde was added to 1 mole of an alkyl hydrazone in a three-necked flask fitted with a thermometer, dropping funnel, reflux condenser, and stirrer, at such a rate that the temperature of the reaction mixture did not exceed 50–60° C. The mixture darkened. Stirring with heating to 60° C was continued for 1 hr, and then the reaction mixture was cooled to room temperature and mixed with powdered potassium carbonate. After drying over granulated K_2CO_3, the mixture was distilled in a current of nitrogen through a vacuum column (12 theoretical plates). The constants of the twice-distilled products (see table) and of the corresponding authentic pyrazolines obtained from crotonaldehyde [7] coincided.

The chromatographic identification of the 5-methyl-2-pyrazolines was carried out on a "Tsvet-1" instrument using glass columns [9] 1.2 m long with stationary liquid phases of different polarities: 18% of diglycerol on Chromosorb W, cyanoethylated mannitol on Celite 545, and 15% of ethanolamine with polyethylene glycol M 400 (1:1) on TNDM.

Condensation of propionaldehyde isopropyl hydrazone with propionaldehyde. After 3 hours' boiling, 22.8 g (0.2 mole) of the hydrazone and 12.5 g (0.25 mole) of the aldehyde in 50 ml of chloroform gave 16.3 g (42%) of a pyrazoline fraction with bp 85–87° C (30 mm). Redistillation yielded 13.7 g of a substance with bp 85.5–86.2° C (30 mm), n_D^{20} 1.4547, mol. wt. 152.9. Its Ir spectrum had two bands of $\nu_{C=N}$ at 1580 and 1628 cm^{-1}, which are characteristic for 2-pyrazolines with and without substituents in position 3[10]. Chromatograms obtained on the columns described above had two peaks, one of which was identical with that of 3-ethyl-1-isopropyl-4-methyl-2-pyrazoline. The PMR spectrum (Fig. 1) contained two HC^3 signals at τ 3.55 and 3.78 ppm and a group of multiplets for HC–N, HC^5, HC^4, and CH_3–C of structures I and II in the τ 6.90–9.45 ppm region.

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