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Abstract

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CHEMISTRY

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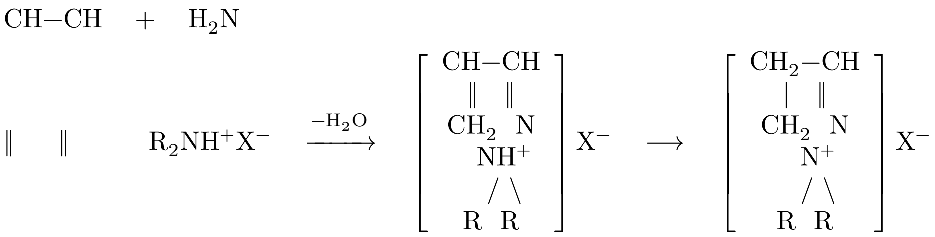
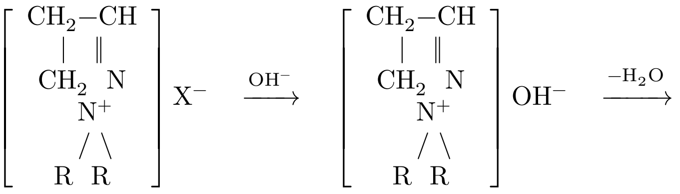
ON THE MECHANISM OF THE AMINONITRILE REARRANGEMENT

(Presented by Academician A. N. Nesmeyanov, February 22, 1962)

We have established that the formation of β-dialkylaminonitriles in the interaction of acrolein with salts of unsymmetrical dialkylhydrazines and subsequent alkalization of the reaction mixture (^{1}) proceeds through the stages of cyclization to pyrazolinium salts and decomposition of quaternary pyrazolinium bases:

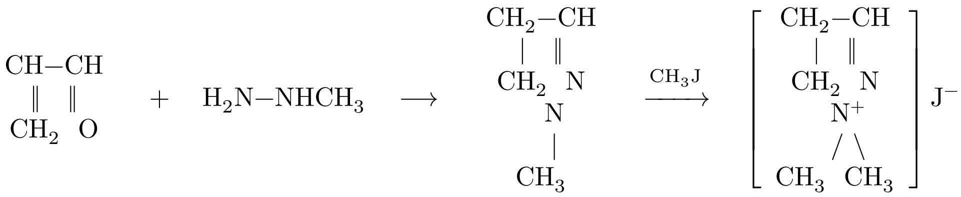


$$\begin{array}{c}\mathrm{CH{-}CH}\\ \parallel\quad\parallel\end{array} + \begin{array}{c}\mathrm{H_2N}\\ \mathrm{R_2NH^+X^-}\end{array} \xrightarrow{-H_2O} \left[\begin{array}{c}\mathrm{CH{-}CH}\\ \parallel\quad\parallel\\ \mathrm{CH_2\quad N}\\ \mathrm{NH^+}\\ /\ \backslash\\ \mathrm{R\quad R}\end{array}\right]X^- \longrightarrow \left[\begin{array}{c}\mathrm{CH_2{-}CH}\\ |\quad\parallel\\ \mathrm{CH_2\quad N}\\ \mathrm{N^+}\\ /\ \backslash\\ \mathrm{R\quad R}\end{array}\right]X^- \qquad (1)$$



$$\left[\begin{array}{c}\mathrm{CH_2{-}CH}\\ |\quad\parallel\\ \mathrm{CH_2\quad N}\\ \mathrm{N^+}\\ /\ \backslash\\ \mathrm{R\quad R}\end{array}\right]X^- \xrightarrow{OH^-} \left[\begin{array}{c}\mathrm{CH_2{-}CH}\\ |\quad\parallel\\ \mathrm{CH_2\quad N}\\ \mathrm{N^+}\\ /\ \backslash\\ \mathrm{R\quad R}\end{array}\right]OH^- \xrightarrow{-H_2O} \begin{array}{c}\mathrm{CH_2{-}C}\\ |\quad\parallel\\ \mathrm{CH_2\quad N}\\ \mathrm{N}\\ /\ \backslash\\ \mathrm{R\quad R}\end{array} \qquad (2)$$

The possibility of ring closure of heterocycles with unsymmetrical dialkylhydrazines by reaction (1) under such mild conditions (mixing of the reagents in the cold) had not previously been suggested by anyone, and the simplest quaternary pyrazolinium salts (II) remained unknown. Their structure was proved by us, using the example of 1,1-dimethylpyrazolinium iodide, by an independent synthesis from methylhydrazine and acrolein according to the scheme:



$$\begin{array}{c}\mathrm{CH{-}CH}\\ \| \quad \|\\ \mathrm{CH_2}\quad \mathrm{O}\end{array} + \mathrm{H_2N{-}NHCH_3} \longrightarrow \begin{array}{c}\mathrm{CH_2{-}CH}\\ | \quad \|\\ \mathrm{CH_2}\quad \mathrm{N}\\ \mathrm{N}\\ |\\ \mathrm{CH_3}\end{array} \xrightarrow{\mathrm{CH_3J}} \left[\begin{array}{c}\mathrm{CH_2{-}CH}\\ | \quad \|\\ \mathrm{CH_2}\quad \mathrm{N}\\ \mathrm{N^+}\\ / \; \backslash\\ \mathrm{CH_3}\quad \mathrm{CH_3}\end{array}\right] \mathrm{J^-} \qquad (3)$$

Methyl iodide salt of 1-methylpyrazoline (VI) proved identical with the product of the interaction of acrolein with an aqueous solution of hydroiodic acid salt of unsymmetrical dimethylhydrazine (II, $R = \mathrm{CH_3}$, $X = \mathrm{J}$). Halide salts of quaternary pyrazolinium bases are very readily soluble in water and crystallize from it with difficulty. 1,1-Dimethylpyrazolinium iodide (VI), on brief heating to 150–180°, decomposes, and among the transformation products aminonitrile is present. The corresponding quaternary bases (III) rearrange smoothly already at the moment of formation in the cold. Upon addition to a concentrated aqueous

to a solution of 1-methylpyrazolinium iodide, β-dimethylaminopropionitrile immediately separates out upon addition of 50% alkali (scheme 2, $\mathrm{R} = \mathrm{CH_3}$, $\mathrm{X} = \mathrm{J}$).

Closure of the pyrazoline ring with formation of quaternary salts proceeds readily in the case of vinyl compounds (acrolein, methyl vinyl ketone). In homologues of acrolein with substituents at the double bond, reaction (1) is arrested at the stage of formation of unsaturated hydrazones (I)[2]. The aminonitrile rearrangement (2) under mild conditions can evidently occur only when hydrogen is present in position 3 of the pyrazoline ring; therefore the pyrazolinium base from methyl vinyl ketone and dimethylhydrazine decomposes with formation of polymers, and not of an aminonitrile[2].

Elucidation of the mechanism of the aminonitrile rearrangement opens broad possibilities for its use for preparative purposes. Indeed, quaternary pyrazolinium salts can be obtained not only from unsymmetrical dialkylhydrazines (I), but also by alkylation of various readily available pyrazolines. This second route makes it possible to obtain pyrazolinium salts with different substituents in the ring and, through them, various difficultly accessible β-aminonitriles, amino acids, β-diamines, and their derivatives.

To illustrate the preparative possibilities of the aminonitrile rearrangement, we carried out the synthesis of β-dimethylaminoisobutyronitrile. First, from methacrolein and methylhydrazine, the previously unknown 1,4-dimethylpyrazoline and 1,1,4-trimethylpyrazolinium iodide were obtained (analogously to scheme 3), and the latter, under the action of alkali, rearranged in the cold to β-dimethylaminoisobutyronitrile (yield 53.5%). This aminonitrile is also formed in the reaction of methacrolein with dimethylhydrazine, but in negligible yield[2].

Experimental Part*

1-Methylpyrazoline. To a solution of 312 g of $NaH_2PO_4 \cdot 2H_2O$ (2 moles) in 600 ml of water was added 92 g (2 moles) of methylhydrazine (b.p. 85.3-85.7° at 760 mm; n_D^{20} 1.4321). To the mixture, freshly distilled acrolein (112 g, 2 moles), which immediately dissolved with strong heating, was added dropwise over the course of half an hour (the flask was cooled externally with ice and salt). After the odor of acrolein had disappeared (after standing for 15 min at room temperature), 200 g of KOH was gradually introduced into the mixture. The separated upper yellowish layer was transferred to a distillation flask and distillate was collected up to 100°. The distillate was salted out with alkali; the organic layer, after drying with alkali, weighed 111 g (n_D^{20} 1.4540). Distillation of it on a column (15 theoretical plates) afforded 96 g (60%) of pure 1-methylpyrazoline with b.p. 109.0-109.4° at 760 mm; d_4^{20} 0.9161; n_D^{20} 1.4548; n_C^{20} 1.4514; Δ_{FC} 122.6; ω_{FCD} 26.96; MR_D found 24.90, calculated 24.89**.

Found, %: N 33.29; 33.54
$C_4H_8N_2$. Calculated, %: N 33.30

1-Methylpyrazoline is a colorless liquid with an odor reminiscent of pyridine. It is miscible with water in all proportions. It does not reduce Fehling' s solution on boiling. Its basic properties are very weakly expressed (on titration with 0.1 N acid in the presence of bromophenol blue it gives no distinct transition point).

1-Methylpyrazoline iodomethylate precipitates as a white crystalline solid immediately upon mixing solutions of methyl iodide (10 ml) and 1-methylpyrazoline (10 g) in three times the volume of benzene. The reaction proceeds with heating and, if the mixture is not cooled with ice or too little benzene is taken, the contents of the beaker may be ejected. After several hours

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* All compounds described, except the aminonitriles, were previously unknown.
** According to Vogel' s bond refractions.

the iodomethylate was filtered off on a Büchner funnel and, after being kept in a vacuum desiccator over paraffin, weighed 26.6 g (quantitative yield). M.p. 141-142° (138-139° from methyl alcohol).

Found, %: N 12.48; 12.19; I (by Folgard) 56.58; 56.68
$C_5H_{11}N_2J$. Calculated, %: N 12.39; I 56.13

β-Dimethylaminopropionitrile from 1-methylpyrazoline iodomethylate. 10 g of unrecrystallized iodomethylate (VI) was dissolved in 10 ml of water, and 20 ml of 50% NaOH was gradually added. With evolution of heat, a colorless liquid separated; after drying over alkali and distillation, 3 g of β-dimethylaminopropionitrile was obtained, b.p. 165-170° at 753 mm; n_D^{20} 1.4235 (literature data: b.p. 171° at 750 mm (^{3}), n_D^{20} 1.4264 (^{1})).

The IR spectrum completely coincided with the spectrum of the authentic preparation (^{1}) in the range 3500-700 cm^{-1}, except for bands at 3350-3450 and 1680 cm^{-1}, indicating a small admixture of water.

The hydrochloride had m.p. 198° (from a mixture of acetone with methyl alcohol) and showed no depression on mixed melting with a known preparation of β-dimethylaminopropionitrile hydrochloride (^{1}).

1,1-Dimethylpyrazolinium iodide from acrolein and dimethylhydrazine. 6 g (0.1 mole) of $H_2NN(CH_3)_2$ was gradually added, with cooling, to 26.5 g of hydriodic acid (analytical grade, sp. gr. 1.53). The salt solution had pH 4-5 (indicator paper). To it was added dropwise 6.5 g (0.12 mole) of freshly distilled acrolein, and the mixture was placed in a vacuum desiccator with P_2O_5. After one day, salt crystals began to separate from the brown solution, and after 3 days the salt had been brought to constant weight, 22.3 g (theoretical yield of $C_5H_{11}N_2J$ 22.6 g). After two recrystallizations from methyl alcohol, the salt had m.p. 137-138° and did not give a depression of the melting point in a mixture with iodomethylate from 1-methylpyrazoline.

Found, %: I 56.48; 56.22
$C_5H_{11}N_2J$. Calculated, %: I 56.13

The IR spectrum of the iodide, recorded by the KBr-pellet method (25 mg per 2 g KBr) on a UR-10 spectrophotometer in the range from 2400 to 700 cm^{-1}, proved to be completely identical with the spectrum of 1-methylpyrazoline iodomethylate and differed sharply from the spectrum of the isomeric β-dimethylaminopropionitrile hydriodide (m.p. 124-125°).

Decomposition of 1-methylpyrazoline iodomethylate on heating to 150-180° for half an hour leads to darkening of the melt, lowering of the melting point to approximately 80°, and a sharp change in the IR spectrum, in which bands appear that are characteristic of β-dimethylaminopropionitrile hydriodide (2262 cm^{-1} −CN group, 1310, 1263, 1242, 1183, 1049, 865 cm^{-1}).

1,4-Dimethylpyrazoline was obtained from methacrolein and methylhydrazine (1 mole each) under the same conditions as 1-methylpyrazoline. After distillation on a column (12 theoretical plates) in a stream of nitrogen, 48.5 g (49%) of pure substance was obtained, b.p. 120.5-121.5° at 749 mm; d_4^{20} 0.8802; n_D^{20} 1.4472; n_C^{20} 1.4439; Δ_{FC} 117.6; ω_{FCD} 26.30. MR_D found 29.81, calculated 29.54.

Found, %: N ~28.63; 28.88
$C_5H_{10}N_2$. Calculated, %: N 28.55

1,4-Dimethylpyrazoline resembles in its properties the 1-methylpyrazoline described above, differing from the latter by its poor solubility in water and yellow coloration.

Iodomethylate of 1,4-dimethylpyrazoline was prepared from the free base in the same way as the iodomethylate of 1-methylpyrazo-

with a 90% yield. Colorless fine crystals with m.p. 117-118° (after recrystallization from methyl alcohol).

Found, %: N 11.90; 11.74; I 52.52; 52.60

$C_6H_{13}N_2I$. Calculated, %: N 11.63; I 52.85

β-Dimethylaminoisobutyronitrile. 47.5 g (0.2 mole) of 1,4-dimethylpyrazolinium methyl iodide was dissolved in 50 ml of water, and then 25 ml of 50% alkali and 25 g of solid caustic potash were gradually added. The separated upper layer was dried over alkali and distilled on a column under vacuum. This gave 12 g (53.5%) of pure β-dimethylaminoisobutyronitrile. B.p. 59–60° at 10 mm, d_4^{20} 0.8507; n_D^{20} 1.4223. MR_D found 33.54, calculated 33.27.

An authentic sample of β-dimethylaminoisobutyronitrile, prepared by us from methacrylonitrile and dimethylamine (see (4)), had b.p. 58–60° at 10 mm; d_4^{20} 0.8492; n_D^{20} 1.4223.

Literature data (4): b.p. 55–56° at 6 mm, n_D^{25} 1.4210.

The aminonitrile hydrochloride melted at 169° and showed no depression of the melting point in a mixture with the authentic hydrochloride salt.

Literature data for β-dimethylaminoisobutyronitrile hydrochloride: m.p. 171–172° (4).

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named after A. A. Zhdanov

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Note: Figure translations are in progress. See original paper for figures.

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