SYNTHESIS OF 1-METHYLPYRAZOLEALDEHYDES AND 1-METHYL-2-PYRAZOLINEALDEHYDES AND THEIR ACETALS

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The synthesis of 1-methylpyrazolealdehydes and 1-methyl-2-pyrazolinealdehydes and their acetals containing the functional groups in positions 3 and 5 of the heterocycle has been described.

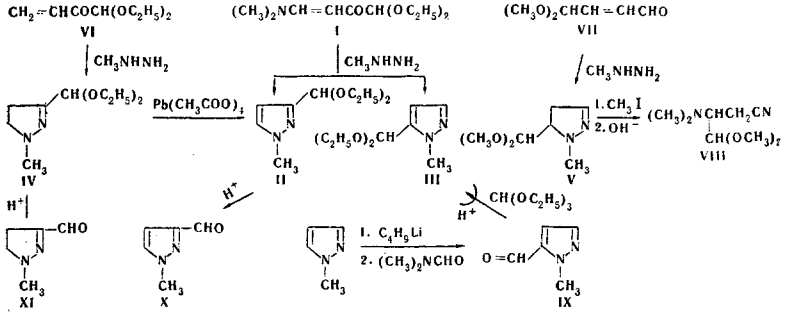
In this work we undertook the synthesis of the previously unknown 1-methylpyrazolealdehydes and 1-methyl-2-pyrazolinealdehydes and their acetals containing the functional groups in positions 3 and 5 of the heterocycles.

The formylation of N-substituted pyrazoles and pyrazolines by the Vilsmeier and Sommelet methods takes place only in positions 4 and 3, respectively [1–3]. The Rosenmund method, which has been applied to the synthesis of 1-arylpyrazole-3-, -4-, and -5-aldehydes [4], requires difficulty accessible starting materials for the N-methyl analogs. Cyclization using α,β-unsaturated aldehydes or their acetals has also been used to prepare N-aryl-substituted and N-unsubstituted pyrazolealdehydes [5–8].

The reaction of monoalkylhydrazines with β-dicarbonyl compounds and their analogs generally leads to mixtures of isomeric 1,3- and 1,5-substituted pyrazoles [9, 10]. However, in the similar closure of the pyrazoline ring this ambiguous course of the reaction was apparently not observed [11, 12].

We reacted β-dimethylaminovinylglyoxal acetal (I) with methylhydrazine. This gave a high yield of an acetal with a low boiling point which, according to thin-layer chromatography, as expected, proved to be a mixture of the 3- and 5-substituted isomers II and III.

In order to synthesize the individual isomers and to identify the respective spots on the chromatogram of the mixture, two methods were used. The individual acetals of 1-methyl-2-pyrazoline-3- and -5-aldehydes (IV and V) obtained, respectively, from vinylglyoxal acetal (VI) and from fumaraldehyde monoacetal (VII), were subjected to oxidation to pyrazoles. Only the oxidation of the 3-substituted isomer with lead tetraacetate took place successfully. The acetal V, the structure of which was confirmed by an aminonitrile rearrangement [13], proved to be stable both to oxidation with lead tetraacetate and to acid hydrolysis.*



1-Methylpyrazole-5-aldehyde (IX) was prepared by reacting of 1-methylpyrazol-5-yllithium [15, 16] with dimethylformamide. This aldehyde was converted into an acetal by the usual method for the purpose of chromatographic identification of the mixture of acetals obtained by cyclization.

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*The peculiarity of this acetal is also shown in the considerable depression of the molecular refraction that is characteristic for pyrazolines sterically loaded in postion 5 [14]. It is an interesting fact that the acetal of β-cyano-α-dimethylaminopropionaldehyde (VIII) obtained as a result of this rearrangement is also stable to acid hydrolysis.

EXPERIMENTAL

All the experiments with pyrazolines, and also the preparation of 1-methylpyrazole-5-aldehyde were carried out in an atmosphere of argon. Melting points were determined on a Kofler block. The IR spectra of the substances were recorded in the form of films on a UR-20 spectrometer.

1-Methyl-2-pyrazoline-3-aldehyde diethyl acetal (IV). A solution of 2.85 g (0.062 mole) of methylhydrazine in 20 ml of water was treated with 5.23 g (0.033 mole) of vinylglyoxal diethyl acetal [17]. After 12 hr, the reaction product was extracted with ether, dried with potassium carbonate, and distilled. The yield of IV was 4.77 g (78%); it yellowed on storage. Bp 95–97° C (8 mm); n_D^{20} 1.4540. Found, %: C 57.98, 58.05; H 9.97, 9.87; N 15.17, 15.21. MR_D 51.90. Calculated for $C_9H_{18}N_2O_2$, %: C 58.20; H 9.68; N 15.01. MR_D 52.02. IR spectrum: 1610 cm^{-1} (C=N). The methiodide underwent no change under the conditions of the aminonitrile rearrangement [13]. Under the conditions of Hofmann degradation [18], a small amount of an unstable reaction product was obtained whose IR spectrum included bands at 1570 cm^{-1} (C=N) and 1630 cm^{-1} (C=C), which are characteristic for unsaturated hydrazones.

1-Methyl-2-pyrazoline-3-aldehyde (XI). The acetal IV, 3.33 g, was dissolved in 18 ml of 1 N HCl. After 3 hr the solution was made alkaline with potassium carbonate, and the hydrolysis product was extracted with ether, dried, and distilled. Yield 1.27 g (63%), bp 70–73° C (3 mm); n_D^{20} 1.5410. IR spectrum: 1655 cm^{-1} (C=O). Positive reaction for an aldehyde with Tollens reagent. Hydrochloride of the oxime, mp 162–163° C (from absolute ethanol). Found, %: Cl 21.90, 21.85. Calculated for $C_5H_9N_3O \cdot HCl$, %: Cl 21.70.

1-Methyl-2-pyrazoline-5-aldehyde dimethyl acetal (V). This was obtained from fumaraldehyde dimethyl monoacetal [19, 20] in a manner similar to that used for the preceding compound. Yield 64% of a product which yellowed on storage. Bp 95–98° C (18 mm); n_D^{20} 1.4525; MR_D 41.05. Calculated: MR_D 41.92. IR spectrum: 1595 cm^{-1} (C=N). In addition to the acetal, a substance was isolated with bp 104–109° C (10 mm), n_D^{20} 1.4760, which, judging from the IR spectrum, was the methylhydrazone of the initial aldehyde: 1592 cm^{-1} (C=N), 1648 cm^{-1} (C=C), 3400 cm^{-1} (N—H). Under the conditions of the aminonitrile rearrangement [13] the methiodide of acetal V (mp 120–121° C) formed the dimethyl acetal of β-cyano-α-dimethylaminopropionaldehyde with a yield of 98%. Bp 86° C (4 mm); n_D^{20} 1.4430. Found, %: C 55.38, 55.44; H 9.47, 9.42; N 15.98, 16.02. Calculated for $C_8H_{16}N_2O_2$, %: C 55.58; H 9.30; N 16.25. IR spectrum: 2255 cm^{-1} (C≡N). This substance and the initial acetal did not change when treated with acid under the conditions mentioned for IV. On being boiled with an acid, acetal V resinified.

1-Methylpyrazole-3-aldehyde diethyl acetal (II). With stirring, 15.2 g (0.034 mole) of lead tetraacetate was slowly added to 5.53 g (0.03 mole) of IV in 30 ml of dry benzene. After 2 hr 30 min the precipitate was filtered off and the filtrate was distilled. Yield 4.26 g (78%), bp 101–104° C (3 mm); n_D^{20} 1.4645. Found, %: C 58.42, 58.21; H 8.55, 8.42; N 15.33, 15.21. Calculated for $C_9H_{16}N_2O_2$, %: C 58.70; H 8.70; N 15.20.

1-Methylpyrazole-3-aldehyde (X). The hydrolysis of acetal II was carried out as described above for XI. Yield 75%. Bp 72–74° C (2 mm); n_D^{20} 1.5132. Found, %: C 53.95, 54.12; H 5.56, 5.91; N 25.24, 25.37. Calculated for $C_5H_6N_2O$, %: C 54.50; H 5.45; N 25.45. IR spectrum: 1685 cm^{-1} (C=O).

1-Methylpyrazole-5-aldehyde (IX). At −10° C, 5.8 g (0.1 mole) of butyllithium in 40 ml of petroleum ether was added to a solution of 6.60 g (0.08 mole) of 1-methylpyrazole in 40 ml of absolute ether. The suspension was stirred at room temperature for 1 hr 30 min and then 8.03 (0.11 mole) of dimethylformamide in 10 ml of absolute ether was added. The mixture was heated to the boil over an hour, left overnight, decomposed with acid, and extracted with ether. The ethereal extract was dried with magnesium sulfate and distilled. Yield 3.78 g (43%), bp 50–53° C (4 mm); n_D^{20} 1.5012. IR spectrum: 1705 cm^{-1} (C=O). Hydrochloride of the oxime, mp 164.5–165.5° C (from ethanol). Found, %: Cl 21.72, 21.79. Calculated for $C_5H_7N_3O \cdot HCl$, %: Cl 21.95.

1-Methylpyrazole-5-aldehyde diethyl acetal (V). A few drops of a 30% ethanolic solution of hydrogen chloride was added to a mixture of 1.1 g (0.01 mole) of aldehyde IX and 1.6 g (0.011 mole) of orthoformic ester in 5 ml of absolute ethanol. After 20 hr, the mixture was distilled. Yield 1.29 g (71%), bp 86–90° C (1 mm); n_D^{20} 1.4690.

Reaction of dimethylaminovinylglyoxal diethyl acetal [17] with methyl hydrazine. This was carried out as described by Bredereck et al. [8] with 30% excess of methylhydrazine sulfate. Yield 81%; bp 92–93° C (1 mm); n_D^{20} 1.4667. Found, %: C 58.38, 58.51; H 9.18, 9.13; N 15.41, 15.42. Calculated for $C_9H_{16}N_2O_2$, %: C 58.70; H 8.70; N 15.20. On chromatography in a thin nonfixed layer of alumina (ether) together with the individual acetals II and III, two spots with R_f 0.68 (II) and 0.79 (III) were found.

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