REACTION OF 1-ARYL-Δ^2-PYRAZOLINE SALTS WITH LITHIUM ALUMINUM HYDRIDE

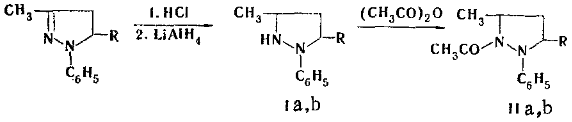
G. A. Golubeva, L. A. Sviridova,
N. Yu. Lebedenko, and A. N. Kost

UDC 547.772.2'778

The corresponding pyrazolidines were obtained by reduction of 1-aryl(1-hetaryl)pyrazoline salts. The structure of the products and the reaction mechanism are discussed.

As we have already reported [1], polarization of the C = N bond in Δ^2-pyrazoline bases is in most cases insufficient for nucleophilic attack. An exception to this is the reaction of 1-alkyl-Δ^2-pyrazolines with organolithium compounds [2]. The formation of an electron-acceptor center on the primary nitrogen atom during protonation or quaternization of the pyrazoline ring should have insured a considerable deficit in the electron density in the 3 position, a deficit sufficient for the addition of a nucleophilic agent such as the hydride ion.

In fact, we observed that 1-phenyl-Δ^2-pyrazoline hydrochlorides are readily reduced by lithium aluminum hydride in absolute ether or tetrahydrofuran to the corresponding arylpyrazolidines, although the bases of these same pyrazolines were recovered unchanged after refluxing for many hours with lithium aluminum hydride (in the same solvents). In view of the facile oxidation of pyrazolidines, we usually acylated the reaction mixture immediately and isolated the pyrazolidines in the form of acyl derivatives in an overall yield of 40-50%.



I, IIa R=H; b R=C_6H_5

The structure of 1-phenyl-3-methylpyrazolidine (Ia) was confirmed by comparison of its hydrochloride with a sample of known structure, obtained by reduction of 1-phenyl-3-methyl-5-pyrazolidone with lithium aluminum hydride [3].

The new method makes it possible to obtain 3,5-disubstituted 1-phenylpyrazolidines; this is not possible in the case of reduction of 3- or 5-pyrazolidones [4].

The IR spectra of the 1-phenyl-2-acetylpyrazolidines obtained by this route do not contain the absorption band at 1580-1620 cm^{-1} that corresponds to the C = N stretching vibrations, but the intense absorption band of an amide group appears at 1660-1680 cm^{-1}.

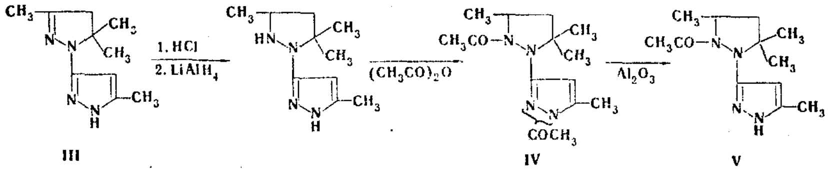
The signal of the 3-CH_3 group in the PMR spectrum of acetylpyrazolidine IIb is shifted to strong field (1.57 instead of 2.5 ppm for the pyrazoline), and splitting in the doublet (J = 3.5 Hz) appears due to interaction with the newly developed 3-H proton (~ 5 ppm). In addition, the signal of the methyl group of the acetyl residue appears as a singlet at 2.25 ppm.

It was found that a similar route can be used to reduce the C = N double bond in 1-hetarylpyrazolines. For example, the diacetyl derivative of 3,5,5-trimethyl-1-(5-methyl-3-pyrazolyl)pyrazolidine (IV) was obtained by the action of lithium aluminum hydride on the hydrochloride of 3,5,5-trimethyl-1-(5-methyl-3-pyrazolyl)pyrazoline (III), which we described in [5], with subsequent acylation; the acyl group attached

---

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 547-550, April, 1973. Original article submitted March 14, 1972.

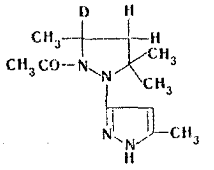
to the pyrazole ring was removed by chromatography with a column filled with Al_2O_3. In this way, we isolated 3,5,5-trimethyl-2-acetyl-1-(5-methyl-3-pyrazolyl)pyrazolidine (V) – the first representative of 1-hetarylpyrazolidines.



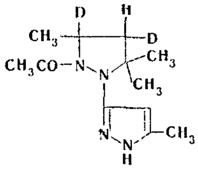
III IV V

In contrast to the starting III, V has an absorption band at 1640 cm^{-1}, which corresponds to the amide carbonyl group of the acyl residue, in its IR spectrum; the UV spectrum corresponds to the spectra of aminopyrazoles [6]. The PMR spectrum of V contains a 3-CH_3 doublet (1.45 ppm, $J = 3.5$ Hz) and a singlet from the CH_3CO group (2.20 ppm). The signals of the 4-CH_2 protons form a system of the ABX type with the 3-H proton; in this system, the X proton (3-H) has a chemical shift of 4.2 ppm, while the AB protons give a multiplet at 1.54-2.10 ppm ($J_{AB} = 12$ Hz). The signals of the protons of the pyrazole portion of the molecule lie in the same region as in the spectrum of the starting material (1.95, 5.54, and 9.6 ppm); this indicates that protonation and, consequently, reduction of the pyrazole ring do not occur [7, 8].

Attack of the proton may thus proceed only at the pyrazoline ring, in which protonation, depending on the conditions, occurs at the $N_{(1)}$, $N_{(2)}$, or $C_{(3)}$ atoms [9-11]. The reduction of the hydrochloride of III with lithium aluminum hydride and subsequent decomposition with deuterium oxide should have led to structures VI or VII, depending on the site of protonation:

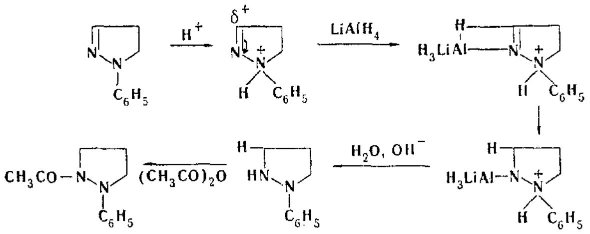


VI



VII

The signal of the 3-H proton (4.20 ppm) vanishes in the PMR spectrum of the reduction product, while the 3-CH_3 group gives a singlet (1.48 ppm), and the spectrum of the 4-CH_2 group takes on the form of an AB system (1.78 and 2.02 ppm, $J = 12$ Hz); this is in agreement with structure VI. The results make it possible to suppose that protonation of not only 1-alkyl and 1-aryl- but also of 1-hetarylpyrazolines occurs primarily at $N_{(1)}$. This sort of protonation of the pyrazoline ring leads to an increase in the polarization of the C=N bond. The reaction then proceeds via the usual scheme of nucleophilic addition under the influence of lithium aluminum hydride.



EXPERIMENTAL

The UV spectra of ethanol solutions were recorded with a Cary spectrophotometer. The IR spectra of the liquid compounds and of mineral oil suspensions of the solid compounds were recorded with IKS-22 and UR-20 spectrometers. The PMR spectra of carbon tetrachloride solutions were recorded with Varian T-60 and XL-100 spectrometers with hexamethyldisiloxane as the internal standard. The course of the reactions and the purity of the products were monitored by thin-layer chromatography on aluminum oxide with benzene–cyclohexane–methanol (10 : 10 : 1).

General Method for the Reduction. A stream of dry hydrogen chloride was passed into a solution of ~0.01 mole of 1-arylpyrazoline in 30-50 ml of absolute ether or tetrahydrofuran for 15 min, after which the solvent was removed by distillation. Dry benzene (50 ml) was added to the residue and then removed by vacuum distillation. This operation was repeated twice. A twofold excess of a suspension of lithium aluminum hydride in 25 ml of ether or tetrahydrofuran was added in portions with stirring to a suspension of the 1-arylpyrazolidine hydrochloride in 100 ml of ether or tetrahydrofuran, and the mixture was refluxed for 3-4 h and then decomposed with water. The precipitate was removed by filtration and washed three times with ether. The combined extracts were then worked up according to the individual properties of the products.

1-Phenyl-3-methylpyrazolidine. A. A 2-g (0.012 mole) sample of 1-phenyl-3-methylpyrazoline in ether was reduced, and a stream of hydrogen chloride was passed into the ether extract obtained after decomposition until precipitation ceased. The precipitate was removed by filtration, washed with ether, and recrystallized from absolute alcohol to give 1.35 g (51%) of 1-phenyl-3-methylpyrazolidine hydrochloride with mp 183°. No melting-point depression was observed for a mixture of this product with a sample of known structure.

B. A 1.9-g (0.011 mole) sample of 1-phenyl-3-methylpyrazoline in ether was reduced, and the combined ether extracts were evaporated to 25 ml and treated with 30 ml of acetic anhydride. The solvent residues were removed by distillation, the residue was refluxed for 4 h, and the acetic anhydride was removed by distillation. The residue was recrystallized from heptane to give 0.9 g (37%) of 1-phenyl-2-acetyl-3-methylpyrazolidine with mp 94°. Found: C 70.6; H 7.6%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.8%. UV spectrum, λ_{max}, nm (log ε): 238 (4.12), 287 (3.13). IR spectrum: 1650 cm^{-1}. PMR spectrum,* δ, ppm: 1.67 (d, 3H), 2.27 (s, 3H), 1.83-2.47 (m, 2H), 3.5-4.15 (m, 2H), 4.59 (m, 1H), 7.13-7.57 (m, 5H).

1,3-Diphenyl-2-acetylpyrazolidine. A 3-g (0.013 mole) sample of 1,3-diphenylpyrazoline in tetrahydrofuran was reduced, and the combined ether extracts were acylated as in the preceding experiment (B). The acetic anhydride was removed by distillation, and the residue (3.5 g) was separated preparatively in a thick layer (1.5 mm) of aluminum oxide with benzene–cyclohexane–methanol (10 : 10 : 1) with collection of the fraction with R_f 0.24. This fraction was recrystallized from petroleum ether to give 1.5 g (42%) of a product with mp 66°. Found: C 76.2; H 6.8%. $C_{17}H_{18}N_2O$. Calculated: C 76.5; H 6.8%. UV spectrum, λ_{max}, nm (log ε): 240 (4.12), 277 (3.57), 350 (2.93). IR spectrum: 1680 cm^{-1}.

1,5-Diphenyl-2-acetyl-3-methylpyrazolidine. A 1.8-g (0.008 mole) sample of 1,5-diphenyl-3-methylpyrazoline in tetrahydrofuran was reduced, and the product was acylated with acetic anhydride by the method presented for 1-phenyl-3-methylpyrazolidine. The acetic anhydride was removed by distillation, and the residue (~2 g) was separated preparatively in a thick layer (1.5 mm) of aluminum oxide with benzene–chloroform (2 : 1). The fraction with R_f 0.24 was collected to give 0.98 g (46%) of a viscous light-yellow oily substance. Found: C 77.1; H 7.1%. $C_{18}H_{20}N_2O$. Calculated: C 77.3; H 7.2%. UV spectrum: λ_{max} 238 nm (log ε 3.91). IR spectrum: 1668 cm^{-1}. PMR spectrum, δ, ppm: 1.57 (d, 3H, J = 3.5 Hz), 2.25 (s, 3H), 2.10-2.57 (m, 3H), 5.0 (m, 1H), 7.0-7.7 (m, 10H).

3,5,5-Trimethyl-2-acetyl-1-(5-methyl-3-pyrazolyl)pyrazolidine. A 3.8-g (0.019 mole) sample of 3,5,5-trimethyl-1-(5-methyl-3-pyrazolyl)pyrazoline in absolute tetrahydrofuran was reduced, and the product was acylated with acetic anhydride by the general method. The residue was recrystallized from petroleum ether to give 1.6 g (37%) of the diacetyl derivative with mp 104°. Found: C 60.2; H 7.9%. $C_{14}H_{22}N_4O_2$. Calculated: C 60.4; H 7.9%. UV spectrum, λ_{max}, nm (log ε): 233 (3.93), 265 (3.99). IR spectrum: 1730, 1670 cm^{-1}. PMR spectrum, δ, ppm: 1.10 (s, 3H), 1.27 (s, 3H), 1.33 (d, 3H, J = 3.5 Hz), 1.84 (s, 3H), 2.10-2.40 (m, 2H), 2.43 (s, 3H), 2.48 (s, 3H), 4.40 (m, 1H), 5.79 (s, 1H).

The diacetyl derivative was chromatographed with a column filled with aluminum oxide (l = 50 cm, d = 2.5 cm) by elution with chloroform–benzene (1 : 1). The eluate was evaporated, and the residue was recrystallized from hexane to give a product with mp 126°. Found: C 60.8; H 8.3%. $C_{12}H_{20}N_4O$. Calculated: C 61.0; H 8.5%. UV spectrum: λ_{max} 220 nm (log ε 4.00). IR spectrum: 3300, 1645 cm^{-1}. PMR spectrum, δ, ppm: 1.05 (s, 3H), 1.1 (s, 3H), 1.45 (d, 3H), 1.54-2.02 (m, 2H), 1.95 (s, 3H), 2.20 (s, 3H), 4.20 (m, 1H), 5.54 (s, 1H), 9.70 (s, 1H).

---

*The following abbreviations are used here and elsewhere: s is singlet, d is doublet, q is quartet, and m is multiplet.

3-Deutero-3,5,5-trimethyl-2-acetyl-1-(5-methyl-3-pyrazolyl)pyrazolidine. A 1.35-g (0.007 mole) sample of 3,5,5-trimethyl-1-(5-methyl-3-pyrazolyl)pyrazoline in absolute tetrahydrofuran was reduced with 0.8 g (0.021 mole) of lithium aluminum hydride, after which the mixture was decomposed with 2.5 ml of deuterium oxide, and the product was acylated with acetic anhydride by the usual method. The residue was recrystallized from petroleum ether to give 0.8 g (41%) of the diacetyl derivative with mp 104°. The diacetyl derivative was chromatographed via the preceding method to give a substance with mp 126°. PMR spectrum, δ, ppm: 1.05 (s, 3H), 1.10 (s, 3H), 1.48 (s, 3H), 1.78 (q, 1H, J = 12 Hz), 1.95 (s, 3H), 1.98 (q, 1H), 2.20 (s, 3H), 5.54 (s, 1H), 9.70 (s, 1H).

1,5-Diphenyl-2-benzoylpyrazolidine. A 3-g (0.013 mole) sample of 1,5-diphenylpyrazoline in tetrahydrofuran was reduced, after which the combined extracts were evaporated and the residue was subjected to Schotten–Baumann benzoylation. Sodium bicarbonate was added to the reaction mixture, and it was extracted with ether. The ether extract was dried with magnesium sulfate, and the ether was removed by distillation. The residue was separated preparatively in a thick layer (1.5 mm) of aluminum oxide with benzene–methanol (10 : 1). The fraction with R_f 0.7 was collected and recrystallized from petroleum ether to give 0.9 g (21%) of a product with mp 80° (dec.). Found: C 80.5; H 6.2%. $C_{22}H_{20}N_2O$. Calculated: C 80.4; H 6.1%. UV spectrum: λ_{max} 227 nm (log ε 3.50). IR spectrum: 1660 cm^{-1}.

LITERATURE CITED

1. A. N. Kost, G. A. Golubeva, M. A. Lapitskaya, and S. M. Sernikova, Zh. Organ. Khim., 5, 752 (1969).
2. A. N. Kost, G. A. Golubeva, M. A. Lapitskaya, and A. G. Popova, Zh. Organ. Khim., 8, 1320 (1972).
3. P. Bouchet, J. Elguero, and R. Jacquier, Tetrahedron, 22, 2461 (1966).
4. G. A. Golubeva, Yu. N. Portnov, A. N. Kost, and L. A. Sviridova, Khim. Geterotsikl. Soedin., 118 (1971).
5. A. N. Kost, G. A. Golubeva, L. A. Sviridova, I. I. Grandberg, and N. B. Chernyshova, Dokl. Akad. Nauk SSSR, 179, 337 (1968).
6. I. I. Grandberg, Zh. Obshch. Khim., 33, 519 (1963).
7. A. V. El'tsov and Nabil Mahmud Omar, Zh. Organ. Khim., 4, 711 (1968).
8. A. V. El'tsov and Nabil Mahmud Omar, Zh. Organ. Khim., 4, 1294 (1968).
9. J. Elguero, R. Jacquier, and C. Marzin, Tetrahedron Lett., 3099 (1970).
10. P. Bouchet, J. Elguero, and R. Jacquier, Tetrahedron Lett., 6409 (1966).
11. J. Elguero and R. Jacquier, Tetrahedron Lett., 1175 (1965).