ACETYLENE DERIVATIVES OF HETEROCYCLES. SOME REACTIONS OF 3-ETHYNYLPYRAZOLE

M. S. Shvartsberg, I. L. Kotlyarevskii, and B. G. Kruglov

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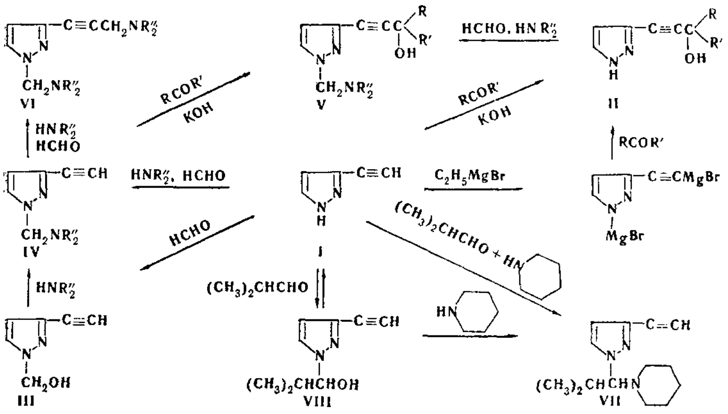
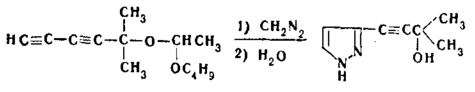
3-Ethynylpyrazole, which possesses two mobile hydrogen atoms, takes part in the Favorskii and Iotsich reactions at the acetylene group and in the Mannich reaction at the acetylene group and the nitrogen atom. It has been found that the pyrazoles are also capable of undergoing aminoalkylation at the nitrogen atom under the action of isobutyraldehyde and secondary amines. The intermediate product of the condensation of isobutyraldehyde with 3-ethynylpyrazole is unstable and exists in equilibrium with the initial compounds.

Only isolated representatives of acetylene derivatives of heterocycles with two and more heteroatoms have been synthesized, and in spite of the fact that the combination of an acetylene radical and a heterocycle must impart special features to these particular compounds, their chemical properties have not been studied at all.

In the present paper we give a preliminary account of some properties of 3-ethynylpyrazole (I) [1]. The reactions performed are shown in the diagram.



The reaction of the pyrazole I with ethylmagnesium bromide gave a dimagnesium derivative, which formed the acetylenic alcohols II with aldehydes and ketones. The pyrazole I has an acidic hydrogen atom on the nitrogen, but in addition to this it undergoes the Favorskii reaction with ketones, giving the alcohols II. This reaction takes place comparatively slowly, and attempts to achieve the decomposition of an alcohol II in the presence of alkaline agents—the so-called "reverse Favorskii reaction"—have not yet been successful. The structure of the alcohols II is not a matter of doubt and is confirmed, not only by the elementary analysis, but also by the presence of a band of the stretching vibrations of the C≡C bond and the absence of the band of a ≡C—H bond in the IR spectra, by their further reactions with the participation of the hydrogen on the nitrogen of the pyrazole ring, and also by the formation of one of them as a product, although not the only one, in the addition of diazomethane to the acetal obtained from butadiynyl dimethyl carbinol and butyl vinyl ether and subsequent saponification.



It is known that pyrazoles are capable of undergoing the Mannich reaction with formaldehyde and secondary amines [2–4]. With formaldehyde under mild conditions, 3-ethynylpyrazole (I) gave a high yield of the alcohol III, which was then smoothly converted into the amines IV. The reaction is easily carried out in one stage. Similarly, the alcohols II gave amino alcohols of the type of V (shown on the basis of compound V with $R = R' = CH_3$ and R''—R'' equal to $-(CH_2)_5-$], which canbe synthesized independently from the aminoacetylenes IV by the Favorskii reaction. The pyrazole I, which is a monosubstituted acetylene, forms Mannich bases not only at the nitrogen of the nucleus but also at the acetylene group (the diamines VI), although under more severe conditions using a catalyst. In the literature the Mannich reaction is described for a series of pyrazoles with the participation of only a single carbonyl-containing reagent—formaldehyde. We have found that the pyrazole I is converted into the amine VII by aminoalkylation with isobutyraldehyde and piperidine. In contrast to the methylol III, the intermediate compound VIII is extremely unstable and is in equilibrium with the initial compounds. On storage, it is gradually converted into the initial I, and this also occurs when it is sublimed in vacuum.

Following information in the literature [5, 6], we ascribe the structure of 1,3-disubstituted derivatives to all the pyrazoles synthesized having a substituent on the nitrogen atom. Since the position of the substituents was not demonstrated conclusively in any of the papers cited, we proposed to return to this question subsequently.

EXPERIMENTAL

Preparation of the pyrazolylacetylenic alcohols II by the Iotsich reaction. With cooling 4.6 g (0.079 mole) of acetone in 5 ml of ether was added dropwise to the Iotsich complex prepared from 1.6 g (0.067 g-atom) of Mg, 7.5 g (0.069 mole) of C_2H_5Br, and 3 g (0.033 mole) of the pyrazole I (mp 55°–56° C [6]) in 35 ml of ether, the mixture was stirred for 12 hr, and then 20 ml of benzene was added and it was boiled for 1 hr. With ice cooling, the mass was decomposed with 10 ml of water, the ethereal-benzene layer was separated off, and the residue was extracted with ether. The aqueous layer was neutralized with hydrochloric acid and extracted again. After drying of the solution with potassium carbarate and elimination of the solvent, the product was distilled in vacuum. The yield of the alcohol II ($R = R' = CH_3$) was 2.5 g (51%), mp 114.5°–115° C (from CCl_4 and CH_2ClCH_2Cl), bp 153°–156° C (2 mm). Found, %: N 18.74. Calculated for $C_8H_{10}N_2O$, %: N 18.66.

The following alcohols II were obtained similarly: $R = CH_3$, $R' = C_6H_5$; yield 53.7%, mp 151°–151.5° C (decomp., from CCl_4). Found, %: N 13.32. Calculated for $C_{13}H_{12}N_2O$, %: N 13.20. $R = (CH_3)_2CH$, $R' = H$; yield 46.7%, mp 110°–111° C (from CH_2ClCH_2Cl), bp 160°–165° C (1 mm). Found, %: N 17.10. Calculated for $C_9H_{12}N_2O_2$, %: N 17.06.

The 1-pyrazolyl carbinols III and VIII. A mixture of 3.5 g (0.038 mole) of the pyrazole I and 5.8 ml of formaline in 8 ml of CH_3OH was stirred at 20° C for 3–4 hr, the solvent was distilled off in vacuum, and the residue (4.3 g) was recrystallized from 6–7 ml of C_6H_6; The yield of the carbinol III was 3.9 g (84%), mp 85°–86° C. Found, %: N 23.17. Calculated for $C_6H_6N_2O$, %: N 22.94.

Compound VIII was synthesized similarly, yield 39.3%, mp 76.5°–77.5° C (from C_6H_6). Found, %: N 17.07. Calculated for $C_9H_{12}N_2O$, %: N 17.06. The sublimation of 0.15 g of the carbinol VIII at 65°–70° C (4 mm[yielded 0.08 g (95.2%) of the pyrazole I.

The amines IV, V; and VII. To 3 g (0.024 mole) of the carbinol III in 10 ml of CH_3OH was gradually added 1.8 g (0.025 mole) of $(C_2H_5)_2NH$ in 4 ml of CH_3OH and the mixture was stirred for 5 hr. Distillation yielded 3.8 g (87.5%) of the amine IV ($R'' = C_2H_5$), bp 66°–67° C (1 mm), n_D^{20} 1.5159. Found, %: N 23.60. Calculated for $C_{10}H_{15}N_3$, %: N 23.71.

The amine IV [$R''-R'' = (CH_2)_5$] was synthesized similarly, with a yield of 80.7%, bp 97°–98° C (0.5 mm), n_D^{20} 1.5407. Found, %: N 22.32. Calculated for $C_{11}H_{15}N_3$: %: N 22.21.

The following were obtained by the same method, but without the isolation of the intermediate 1-pyrazolyl carbinols:

a) The amino alcohol V [$R''-R'' = -(CH_2)_5-$] from the alcohol II ($R = R' = CH_3$), yield 82%, mp 84°–85° C (from a mixture of CCl_2 and petroleum ether). Found, %; N 17.07. Calculated for $C_{14}H_{21}N_3O$, %: N 16.99.

b) The amine VII from the pyrazole I (in ether as solvent), yield (unrecrystallized[77.3%, mp 65°–66° C (from C_2H_5OH), bp 98°–99° C (1.5 mm). Found, %: N 17.96. Calculated for $C_{14}H_{21}N_3$, %: N 18.16.

The diamines VI. A mixture of 2.2 g (0.012 mole) of the amine IV ($R'' = C_2H_5$), 0.6 g (0.02 mole) of the paraformaldehyde, 1.5 ml of $(C_2H_5)_2NH$, and 0.015 g of Cu_2Cl_2 in 10 ml of dioxane was heated at 100° C for 3 hr. After cooling, the mass was diluted with 75 ml of ether and washed with dilute (1 : 1) hydrochloric acid. The solution of the hydrochloride was extracted with ether and was then made alkaline with KOH with the simultaneous addition of ice. The diamine VI was extracted with ether and distilled; yield 2.7 g (82.8%), bp 116–118° C (1 mm), n_D^{20} 1.5100. Found, %: N 21.29. Calculated for $C_{15}H_{26}N_4$, %: N 21.35.

Preparation of the alcohols II and V by the Favorskii reaction. At 0° C, 3 g (0.033 mole) of the acetylene I in 30 ml of ether was added to a suspension of 7.4 g (0.13 mole) of KOH in 80 ml of ether at 0° C and then, after 1–2 hr, 3 g (0.05 mole) of acetone in 5 ml of ether, and the mixture was stirred for 2–3 hr, after which the temperature was gradually raised to room temperature. After two days, 10 ml of water was added to the mixture, with cooling, and it was saturated with CO_2 and extracted with ether. The aqueous layer was neutralized with hydrochloric acid and extracted again. Distillation yielded 3.8 g (77.5%) of the alcohol II ($R = R' = CH_3$).

The amino alcohol V ($R = R' = CH_3$) was synthesized similarly from the amine IV [$R''-R'' = -CH_2)_5-$], yield 68.5%.

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Institute of Chemical
Kinetics and Combustion,
Siberian Division, AS USSR,
Novosibirsk