THE ADDITION OF DIAZOMETHANE TO β-ETHYNYLPYRIDINES

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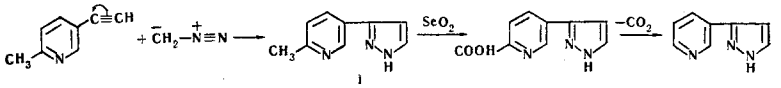
The action of diazomethane on β-ethynylpyridines substituted in the pyridine ring or analogous compounds with an alkyl group in place of the acetylenic hydrogen atom has given 3-(pyridin-3-yl)pyrazoles. When the acetylenic hydrogen atom is replaced by an electron-accepting carboxyl group, the polarization of the triple bond interferes with the reaction, which then leads to a mixture of 3- and 4-(pyridin-3-yl)pyrazoles with the simultaneous methylation of the nitrogen of the pyrazole ring.

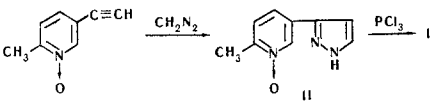
We have effected the synthesis of some 3- and 4-(pyridin-3-yl)pyrazoles by the reaction of 5-ethynyl-2-methylpyridine and its derivatives with diazomethane. There is information in the literature that the action of diazomethane on 5-ethynyl-2-methylpyridine forms 2-methyl-5-(pyrazol-4-yl)pyridine [1]. We have shown that a single substance is formed in this reaction but the pyrazole ring in this compound is attached to the pyridine ring not at the fourth but at the third carbon atom (I). The acid that was isolated when the methyl group was oxidized with selenium dioxide was decarboxylated, and the unsubstituted pyridylpyrazole so formed proved to be identical with 3-[pyrazol-3(5)-yl]pyridine, which has been described previously [2, 3].



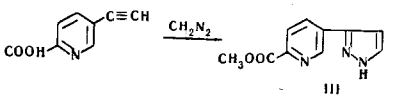
I

The fact that the reaction leads to the formation of the 3-isomer shows that the pyridine ring exerts a -M effect in relation to the acetylenic bond and facilitates the nucleophilic addition reaction. The −I effect of the acetylene group, which is shown in the low basicity of the pyridine nitrogen atom [4], apparently has no substantial effect in this case.

The quaternization of the hetero atom and the introduction of electron-accepting substituents into the pyridine nucleus should also direct the reaction towards the formation of the 3- isomer. Thus, the reaction of 5-ethynyl-2-methylpyridine N-oxide with diazomethane gives a quantitative yield of 2-methyl-5-[pyrazol-3(5)-yl]pyridine N-oxide (II). After the elimination of the N-oxide group, we arrived at a compound identical with the pyrazolylpyridine I.

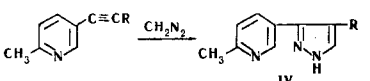


II



III

Similarly, the action of diazomethane on 5-ethynylpicolinic acid gave us methyl 5-[pyrazol-3(5)-yl]picolinate (III) the IR spectrum of which had the characteristic frequency of an ester group in the 1720 cm^{-1} region and lacked the absorption band of an acetylenic bond. The action of diazomethane on pyridylethynylmethanols and pyridylpropargylamines also formed a single isomer in each case. However, the presence of the voluminous substituents on the triple bond sterically hindered addition, and the yields of the corresponding pyridylpyrazoles IV did not exceed 10-30%.



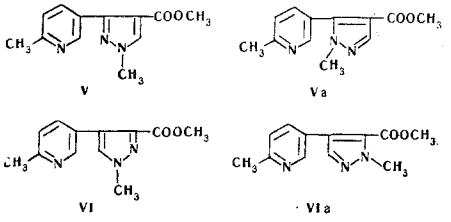
IV

R=−C(OH)$(CH_2)_5$ a; R=−$CH_2N(C_2H_5)_2$ b; R=−CH_2N⟨O⟩ c

The replacement of the acetylenic hydrogen atom by an electron-accepting group such as carboxyl should change the direction of polarization of the triple bond which, in its turn, could lead to the formation of two isomeric pyridyl pyrazoles. In actual fact, the product of the reaction of diazomethane with (2-methylpyridin-5-yl)propiolic acid, according to thin-layer chromatography in alumina, contained two substances with similar R_f values. They could be separated only by preparative chromatography in a nonfixed layer of alumina. Elementary analysis showed that the substances isolated were identical in composition and were, apparently, 2-methyl-5-[4-methoxycarbonyl-1-methylpyrazol-3(5)-yl]pyridine (V) and 2-methyl-5-(3-methoxycarbonyl-1-methylpyrazol-4-yl)pyridine (VI). A study of their IR spectra in carbon tetrachloride showed the absence of N–H stretching vibrations in the 3200-3400 cm^{-1} region. The PMR spectra of the acids obtained after hydrolysis of the corresponding esters confirmed the methylation of one of the nitrogen atoms of the pyrazole ring. We observed a singlet with a chemical shift δ 3.90 ppm corresponding to the protons of the methyl group of N-methylpyrazole [5]. The other signals in the spectrum were assigned in the following way: singlet δ 2.40 ppm – to the protons of an α-methyl group in pyridine; doublet δ 7.19 ppm – to the β-picoline proton (J = 8 Hz); singlet δ 7.53 ppm characteristic for the 3(5)-hydrogen atom of pyrazole; quartet with δ 7.63 ppm corresponding to the γ-proton of the pyridine ring (J = 8 Hz through coupling with the β-picoline proton and J = 2 Hz through coupling with the α-picoline hydrogen); and the doublet with δ 8.33 ppm which is ascribed to the α-picoline proton (J = 2 Hz).

Thus, during the reaction the excess of diazomethane methylates the hydrogen atom of the NH group of the pyrazole ring, which is quite understandable since the presence of an electron-accepting group (COOH, $COOCH_3$) in the pyrazole nucleus must appreciably affect the acidity of a hydrogen atom attached to an atom of the pyrazole nucleus.

In view of what has been said, four structures can be proposed for the two reaction products that we isolated: in the first place they may be position isomers with respect to the pyridine nucleus, i.e., pyridin-3(5)- or -4-ylpyrazoles and in the second case each of these isomers can be methylated at one nitrogen atom of the other:



If our substances had the structures VI and VIa, the hydrolysis of the esters and the decarboxylation of the acids obtained should have given us the same 2-methyl-5-(1-methylpyrazol-4-yl)pyridine. However, the products of hydrolysis and decarboxylation had different chromatographic mobilities and their picrates had different melting points. This shows that the esters that we had isolated consisted of position isomers of the pyridine nucleus with respect to the nitrogen of the pyrazole ring. The IR spectra of the corresponding acids had the frequencies of the vibrations of a C=O group, the frequency for the compound obtained in smaller amount being 1670 cm^{-1}. In the IR spectrum of the second compound the frequency of the C=O group was greater than 1700 cm^{-1}. It is known that the IR spectra of pyridine-2-carboxylic acids have frequencies of the vibrations of the C=O group higher than those of the 3- and 4-carboxylic acids [6] because of the influence of the –M effect of the nitrogen of the pyridine nucleus and also because of the possibility of the formation of intramolecular hydrogen bonds.

Taking what has been said into account, we have ascribed to one ether the structure of 5-[4-methoxycarbonyl-1-methylpyrazol-3-yl]2-methylpyridine (V) and to the other, formed in major amount, the structure of 5-[3-methoxycarbonyl-1-methylpyrazol-4-yl]-2-methylpyridine (VI).

EXPERIMENTAL

Alumina of activity grade II was used for thin-layer chromatography. Preparative chromatography was carried out on 180 × 240 mm plates with a layer of absorbent 2 mm thick. The substances were eluted with ethyl acetate. The benzene–methanol (10 : 1) system was used to check the individuality and separation of the pyridylpyrazoles obtained. The UV spectra were taken on an SF-4 instrument in methanol and chloroform. The PMR spectra were taken on a JNMC-60 instrument with concentrations of the solutions in 2 N caustic potash of ~6%. Paper chromatography was performed on "Leningrad medium" paper.

(2-Methylpyridin-5-yl)propiolic acid. With stirring over 1 hr, a solution of 23.4 g (0.2 mole) of 5-ethynyl-2-methylpyridine in 60 ml of absolute tetrahydrofuran was added to a solution of ethylmagnesium bromide prepared from 4.8 g

(0.2 g-atom) of magnesium and 32.6 g (0.3 mole) of ethyl bromide in 120 ml of absolute tetrahydrofuran, the ethane evolved being collected in a eudiometer (~2.5 *l* was liberated). After the end of the addition, the reaction mixture was heated at 60-70°C for 20 min. Another 1.5 *l* of gas was liberated. The reaction mixture was cooled and, with stirring, finely-crushed solid carbon dioxide was added in small portions. The viscous mass was left for the evaporation of the excess of CO_2, and then, with ice cooling, the residue was decomposed with 48 ml of 2 N HCl. The pH of the mixture was brought to 4.5-5 by the addition of 2 N caustic soda and the acid that precipitated was separated off and recrystallized from methanol. Yield 38 g (58%), mp 231-232°C. Found %: C 67.46, 67.47; H 4.56, 4.64. $C_9H_7NO_2$. Calculated %: C 67.07; H 4.37. R_f on paper in the ethanol ammonia water (20 : 1 : 4) system 0.62. UV spectrum, λ_{max}, nm (log ε): 245 (4.13), 282 (3.93), 332 (1.56).

5-Ethynyl-2-methylpyridine N-oxide. In drops, 60 ml of 27.5% perhydrol was added to 55 g (0.5 mole) of 5-ethynyl-2-methylpyridine. The temperature rose to 30-40°C and then, with vigorous stirring, 51 ml (0.56 mole) of acetic anhydride was added, the addition being regulated in such a way that the temperature did not exceed 60-70°C. The reaction mixture was kept at 60-65°C for 2 hr, and then 2 ml of 40% aqueous formalin was added and it was heated for another 1 hr. The resulting solution was evaporated in vacuum three times with the addition of 100 ml of water each time. The residue was recrystallized from acetone. Yield 42.0 g (64%), mp 158-160°C. Found %: C 72.13, 72.33; H 5.34, 5.35. C_8H_7NO. Calculated %: C 72.10; H 5.20. R_f in a thin layer of alumina 0.59 [benzene-ethanol (9 : 1)]. UV spectrum: λ_{max} 238, 265-268 nm (log ε 4.49, 3.98).

2-Methyl-5-[pyrazol-3(5)-yl]pyridine N-oxide (II). To a solution of 1.33 g (0.01 mole) of 5-ethynyl-2-methylpyridine N-oxide in 10 ml of dimethyl sulfoxide was added 300 ml of an ethereal solution of diazomethane obtained from 30 g of nitrosomethylurea. The mixture was left to stand at room temperature in the dark for 6 days. It deposited crystals which were filtered off with suction and recrystallized from ethanol (1.1 g). Evaporation of the filtrate yielded another 0.6 g of the N-oxide II (the constants and properties of the pyridylpyrazoles obtained here and below are given in the table). R_f in a thin layer of alumina 0.37.

2-Methyl-5-[pyrazol-3(5)-yl]pyridine (I). A) To a solution of 3.5 g (0.03 mole) of 5-ethynyl-2-methylpyridine in 10 ml of ether was added 600 ml of an ethereal solution of diazomethane obtained from 60 g of nitrosomethylurea, and the mixture was left to stand at room temperature in the dark for 3 days. The ether and the unchanged 5-ethynyl-2-methylpyridine were distilled off in vacuum, and the residue was crystallized three times from benzene. Yield 1.9 g (41%), mp 123-124°C, R_f 0.45 (Al_2O_3). Literature data [1]: mp 115-117°C.

B) A mixture of 0.35 g (0.02 mole) of the N-oxide II and 20 ml of chloroform cooled to 0°C was treated with 1 ml of phosphorus trichloride and was then heated at 70-80°C for 1 hr. Then it was cooled, diluted with water, made alkaline with concentrated alkali solution, and extracted with chloroform. The solvent was evaporated off in vacuum and the residue was crystallized from benzene. Yield 0.2 g (64%), mp 123-124.5°C. A mixture with the material obtained from 5-ethynyl-2-methylpyridine gave no depression of the melting point. The chromatographic behaviors of the two substances were also identical.

3-[Pyrazol-3(5)-yl]pyridine. A solution of 1.0 g (0.006 mole) of the pyrazolylpyridine I in 30 ml of dimethyl sulfoxide was treated with 1.11 g (0.01 mole) of selenium dioxide and, with stirring, the mixture was heated to 110-120°C over 20 min. To complete the reaction the temperature was raised to 140-150°C. After cooling, the reaction mixture was filtered, the precipitate of metallic selenium was washed with ethanol, the ethanol and dimethyl sulfoxide were distilled off in vacuum, and the residual oil was triturated in acetone until it became crystalline. The solid matter was filtered off, washed with ether, and recrystallized from water. Yield 0.3 g (23%), mp 250-260°C (decomp.). The substance obtained gave the color reaction with ferrous sulfate that is characteristic for pyridine-2-carboxylic acids [7] and it dissolved in alkali. The acid was decarboxylated by being heated in a vacuum of 15 mm at 250-270°C until the evolution of bubbles of carbon dioxide ceased. The sublimed oil was converted into the picrate, mp 194-196°C (from ethanol) [2], R_f 0.19 (Al_2O_3). Found %: N 22.87, 22.94. $C_3H_7N_3 \cdot C_6H_3N_3O_7$. Calculated %: N 22.60.

2-Methyl-5-[4-R-pyrazol-3(5)-yl]pyridines. To an ethereal solution of 0.01 mole of 2-methyl-5-(2-R-ethynyl)-pyridine was added 200 ml of an ethereal solution of diazomethane obtained from 20 g of nitrosomethylurea, and the mixture was left in the dark at room temperature for 10 days. The ether was evaporated off in vacuum and the pyrazolpyridines obtained were separated from the starting material by preparative chromatography in a thin layer of alumina. The IVa was isolated from the band with R_f 0.64 (colorless crystals), IVb from the band with R_f 0.25 (oil), and IVc from the band with R_f 0.24 (colorless crystals). The constants and yields are given in the table.

Table 1. Substituted Pyridhylpyrazoles

Compound	Mp, °C (solvent)	Empirical formula	Found, %		Calculated, %		Yield, %
			C	H	C	H	
2-Methyl-5-[pyrazol-3(5)-yl] pyridine	241 (ethanol)	$C_9H_9N_3O$	61,65 61,63	5,21 5,10	61,70	5,18	97
5-[4-(1-Hydroxycyclohexyl)pyrazol-3-yl]-2-methylpyridine	150—151 (petroleum ether)	$C_{15}H_{19}N_3O$	69,84 70,07	7,35 7,41	70,00	7,44	16
2-Methyl-5-[4-morpholinomethylpyrazol-3(5)-yl] pyridine	145—146 (hexane)	$C_{14}H_{18}N_3O$	65,14 64,79	7,03 7,02	65,09	7,02	28
5-[4-Diethylaminopyrazol-3(5)-yl]-2-methylpyridine	158—159* (ethanol)	$C_{17}H_{20}N_4 \cdot C_6H_3N_3O_7$	49,90 50,11	4,53 4,80	50,82	4,90	10
Methyl 5-[pyrazol-3(5)-yl]-picolinate	145—146 (petroleum ether)	$C_{10}H_9N_3O_2$	59,18	4,71	59,10	4,46	39
5-[4-Methoxycarbonyl-1-methylpyrazol-3 3(5)-yl]-2-methylpyridine	85—86 (hexane)	$C_{12}H_{13}N_3O_2$	62,17 62,32	5,78 5,81	62,32	5,67	12
2-Methyl-5-[1-methylpyrazol-3(5)-yl] pyridine	227—228* (ethanol)	$C_{10}H_{11}N_3 \cdot C_6H_3N_3O_7$	48,02	3,57	47,76	3,51	31
5-(3-Methoxycarbonyl-1-methylpyrazol-4-yl)-2-methylpyridine	155* (ethanol)	$C_{12}H_{13}N_3O_2 \cdot C_6H_3N_3O_7$**					20
2-Methyl-5-(1-methylpyrazol-4-yl) pyridine	242—243* (ethanol)	$C_{10}H_{11}N_3 \cdot C_6H_{13}N_3O_7$	47,55 47,77	3,56 3,60	47,76	3,51	15

*Figures for the picrates.

†Found %: N 17.78. Calculated %: N 18.26.

5-[4-Methoxycarbonyl-1-methylpyrazol-3-yl]-2-methylpyridine (V) and 5-[3-Methoxycarbonyl-1-methylpyrazol-4-yl]-2-methylpyridine (VI). One liter of an ethereal solution of diazomethane obtained from 100 g of nitrosomethylurea was added to a solution of 4.83 g (0.03 mole) of (2-methylpyridin-5-yl)propiolic acid in 60 ml of dimethyl sulfoxide, and the mixture was allowed to stand at room temperature in the dark for 6 days. The ether and the dimethyl sulfoxide were distilled off in vacuum and the residue was separated preparatively in a thin layer of alumina. The band with R_f 0.51 yielded 800 mg of the crystalline [pyrazol-3-yl]pyridine V. The band with R_f 0.72 yielded 1.3 g of VI.

2-Methyl-5-[1-methylpyrazol-3-yl]pyridine. A mixture of 0.3 g of the [pyrazol-3-yl]pyridine V and 20 ml of 2 N caustic soda solution was boiled for 30 min, cooled, and acidified with conc. HCl to pH 4.5-5; then the aqueous solution was evaporated to dryness and extracted with boiling absolute ethanol. The ethanol was evaporated off in vacuum and the 5-[4-carboxy-1-methylpyrazol-3-yl]-2-methylpyridine was crystallized from ethanol. Yield 0.25 g (89%), mp 160-161°C. R_f on paper in the isopropanol-ammonia-water (10 : 1 : 1) system 0.33; in the ethanol-ammonia-water (20 : 1 : 1) system 0.68. Some 0.2 g of the acid obtained was decarboxylated in vacuum at 200°C, and 50 mg of the oil that sublimed was converted into the picrate, R_f 0.63 (Al_2O_3).

2-Methyl-5-(1-methylpyrazol-4-yl)pyridine. A mixture of 1 g of the (pyrazol-4-yl)pyridine VI and 40 ml of 2 N caustic soda was boiled for 6 hr, cooled, acidified with conc. HCl to pH 4.5, and evaporated to dryness in vacuum. The residue was extracted with boiling absolute ethanol; when the extract was cooled it deposited colorless crystals of 5-(3-carboxy-1-methylpyrazol-4-yl)-2-methylpyridine. Yield 0.7 g (88%), mp 258-260°C (from ethanol), R_f on paper in the isopropanol-ammonia-water (10 : 1 : 1) system 0.63, in the ethanol-ammonia-water (10 : 1 : 4) system 0.82. Some 0.3 g of the acid obtained was decarboxylated at 250-270°C in vacuum, and 100 mg of the oil that sublimed was converted into the picrate, R_f 0.63 (Al_2O_3).

Methyl 5-[pyrazol-3(5)-yl]picolinate (III). A solution of 1.47 g (0.01 mole) of 5-ethynylpicolinic acid in 20 ml of ether was treated with 300 ml of an ethereal solution of diazomethane obtained from 30 g of nitrosomethylurea, and the mixture was left at room temperature in the dark for 6 days. The solvent was evaporated off in vacuum, and the residue was recrystallized from petroleum ether and separated preparatively in a thin layer of alumina in the chloroform-petroleum ether (2 : 1) system. The band with R_f 0.82 yielded 800 mg of the ester III. For its constants and yield, see Table 1.

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