REACTION OF INDAZOLE AND ALKYLPYRAZOLES WITH ACETYLENE

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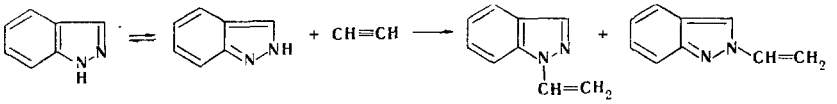
The reaction of indazole and pyrazole and its alkyl-substituted derivatives with acetylene was studied. It was established that indazole and 3(5)-methylpyrazole form a mixture of vinyl isomers corresponding to their tautomeric forms under vinylation conditions. The ratios of the isomers of vinylindazoles in the reaction mixtures depend on the nature of the catalyst. The indazole isomers were separated by gas–liquid chromatography, and the 3(5)-methylpyrazole isomers were separated by vacuum fractionation. 1-Di(1-pyrazolyl)ethanes, the structure of which was confirmed by their PMR spectra, are also formed in the vinylation of pyrazoles.

Until recently, vinylpyrazones were obtained mainly by dehydration of hydroxyethyl derivatives, dehydrochlorination of 1-(β-chloroethyl)pyrazoles, and by reaction of pyrazoles with vinyl acetate [1-3]. The reaction of alkylpyrazoles with acetylene under pressure in the presence of cadmium acetate was described for the first time in a British patent [4].

In the present research we investigated the reaction of acetylene with indazole (I), unsubstituted pyrazole (II), 3(5)-methylpyrazole (III), and 3,5-dimethylpyrazole (IV) under various catalytic conditions in order to synthesize and subsequently separate the resulting isomers of the vinyl derivatives. Potassium hydroxide, the potassium salt of the starting pyrazole, cuprous chloride, and cadmium acetate were used as the catalysts. The vinylation conditions for the investigated compounds and the yields of the final products are presented in Table 1. The reaction proceeds best in dioxane. However, the vinyl derivatives of pyrazoles II-IV evidently form associates with the solvent, and this hinders their isolation. In this connection, the vinylation of II-IV was carried out primarily in benzene.

Considering the tautomeric character of indazole, one might have assumed the formation of a mixture of isomers V and VI when it is vinylated:



I V VI

In fact, 1-vinylindazole (V) and 2-vinylindazole (VI), the amounts and ratio of which in the reaction mixture depend on the nature of the catalyst used, were detected in all of the products of vinylation of indazole I by means of the PMR spectra. Thus, 40% isomer V and 60% isomer VI are formed when potassium hydroxide is used. Replacement of potassium hydroxide by cuprous chloride or cadmium acetate leads to an increase in the percentage of isomer VI to 82 and 94%, respectively. We were unable to isolate individual 1- and 2-vinylindazoles from the high-boiling reaction mixture by vacuum fractionation. Isomers V and VI was used to obtain 1- and 2-ethylindazoles (XI and XII, Table 2). Their physicochemical constants are in agreement with the literature data.

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TABLE 1. Vinylation of Pyrazoles

Starting compound	Catalyst	% catalyst	Reaction temp.	Reaction time, h	Yield, %
I	KOH	30	175—180	2	80*
	CuCl	3—5		2,5	
	$Cd(CH_3COO)_2$	8			
II	KOH	30	160—165	3	79
	CuCl	3—5			
	$Cd(CH_3COO)_2$	8			54
III	CuCl	30	180—185	0,5	80*
	Potassium salts	6		1	
	$Cd(CH_3COO)_2$	8		3	65
IV	KOH	30	160—165	3	84
	CuCl	3—5	180—185	2	63
	$Cd(CH_3COO)_2$	8		2,5	75

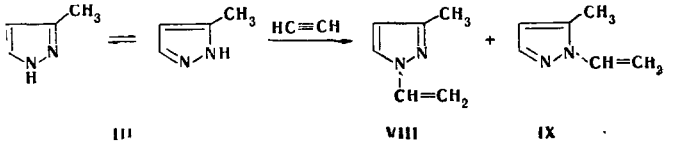
*In dioxane.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	bp °C (mm)	d_4^{20}	n_D^{20}	Literature data
1-Vinylindazole (V)*	78 (4)	—	—	—
2-Vinylindazole (VI)	103 (2)	1,1062	1,6437	—
1-Vinylpyrazole (VII)	63 (50)	1,0133	1,5160	1,2
1-Vinyl-3-methylpyrazole (VIII)	66 (30)	0,9719	1,5125	—
1-Vinyl-5-methylpyrazole (IX)	78 (30)	0,9802	1,5200	—
1-Vinyl-3,5-dimethylpyrazole (X)	76 (15)	0,9623	1,5164	1,2,4
1-Ethylindazole (XI)†	123 (20)	1,0527	1,5521	12
2-Ethylindazole (XII)‡	136 (13)	1,0778	1,5890	12
1-Ethylpyrazole (XIII)	70 (70)	0,9553	1,4685	13
1-Ethyl-3-methylpyrazole (XIV)	85 (78)	0,9238	1,4682	12
1-Ethyl-5-methylpyrazole (XV)	90 (60)	0,9428	1,4739	12
1-Ethyl-3,5-dimethylpyrazole (XVI)	72 (20)	0,9166	1,4710	4

*This compound had mp 36°.
†The picrate had mp 147-149°.
‡This compound had mp 39-49°.

As in the case of indazole, the reaction of methylpyrazole III with acetylene gives a mixture of isomers:



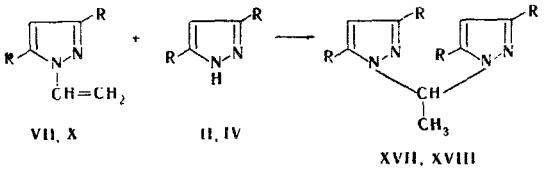
In a recently published paper [5] it was shown that a mixture of 1-vinyl-3-methylpyrazole and 1-vinyl-5-methylpyrazole in a ratio of 60:40 is formed in the reaction of 3(5)-methylpyrazole with acetylene under pressure in presence of pyrazolylsodium. A different ratio (30:70) of these isomers in an analogous reaction was reported in [6]. The mixtures of isomers were not separated to give the individual components in either of the indicated papers. The use of PMR spectroscopy made it possible to establish that the nature of the catalyst has almost no effect on the ratio of the resulting isomers VIII and IX under our investigated conditions for the vinylation of 3(5)-methylpyrazole III (Table 1), and their ratio in the reaction mixture is 60:40 in all cases; this is in agreement with the data in [5]. The mixture of 1-vinyl-3(5)-methylpyrazoles was separated to give individual VIII and IX by vacuum fractionation.

It should be noted that in the vinylation of pyrazoles II-IV in the presence of cuprous chloride and cadmium acetate we were able to isolate 1-di(1-pyrazolyl)ethanes, which were also synthesized by reaction of equimolar amounts of 1-vinylpyrazoles and pyrazoles in the presence of CuCl.

TABLE 3. PMR Spectra of Vinyl Derivatives of Indazole and Pyrazoles

Compound	Chemical shifts, δ, ppm								Spin–spin coupling constants (SSCC), J, Hz					
	3-H	4-H	5-H	H_A	H_B	H_X	CH_3	δ′	3-H, 4-H	4-H, 5-H	H_A, H_B	H_A, H_X	H_B, H_X	long-range SSCC
V	7,90	—	—	4,74	5,61	7,23*	—	0,87	—	—	0,0	8,8	15,2	—
VI	7,88	—	—	4,98	5,85	7,00*	—	0,87	—	—	0,8	8,7	15,4	0,9 (3H, 4H)
VII	7,39	6,19	7,44	4,68	5,38	6,93	—	0,70	1,4	2,6	0,8	9,0	15,8	—
VIII	—	5,93	7,28	4,58	5,29	6,80	2,18	0,71	—	2,4	0,7	8,6	15,4	—
IX	7,24	5,85	—	4,66	5,56	6,80	2,20	0,90	1,4	—	0,0	8,6	15,0	0,9 (CH_3, 4H) 0,5 (CH_3, 3H) 0,7 (3H, H_X)
X	—	5,65	—	4,56	5,48	6,69	2,10† 2,18‡	0,92	—	—	0,0	8,9	15,2	0,6 ($5CH_3$, 4H)

*Superimposed on the signals of the protons of the benzene ring δ^{VI} 6.80-7.61 and δ^{V} 6.90-7.61.
†3-CH_3.
‡5-CH_3.



VII, X II, IV XVII, XVIII

II, VII, XVII R = H; IV, X, XVIII R = CH_3

The presence of a quartet at weak field (δ 6.47 and 6.33 ppm) and of a doublet at strong field (δ 2.04 and 1.98 ppm) with an integral intensity ratio of 1:3 in the PMR spectra of 1-di(1-pyrazolyl)ethane (XVII) and 1,1-bis(3,5-dimethyl-1-pyrazolyl)ethane (XVIII) indicates that the pyrazole rings in them are joined by the $-CHCH_3$ fragment.

The IR spectra of vinylpyrazoles V-X contain intense absorption bands at 960, 1650, and 3110 cm^{-1} corresponding to the vibrations of the vinyl group. The absorption at 1524 and 1566 cm^{-1} corresponds to the vibrations of the pyrazole ring. The bands at 2858, 2910, and 2940 cm^{-1} in the spectra of pyrazoles VIII-X characterize the stretching vibrations of the CH_3 group. The method of paramagnetic additives [7] was used to assign the signals of the protons of the 3-CH_3 and 5-CH_3 groups in the PMR spectra of VIII and IX and also to determine the position of the vinyl group in the vinyl indazole isomers.

The spectra of the investigated vinylpyrazoles (Table 3) have the following features. The J_{AB} constants, which characterize the spin–spin coupling of the β-olefinic protons, are close in value in the spectra of VII and VIII and differ appreciably from the J_{AB} values in the spectra of pyrazoles IX and X. Moreover, the internal chemical shifts ($\delta' = \delta_B - \delta_A$) in the spectra of vinylpyrazoles VII and VIII also coincide but differ from the δ′ values in the spectra of IX and X. The spin–spin coupling of the ring protons with the CH_3 group shows up only in the spectra of vinylpyrazoles IX and X. Long-range spin–spin coupling of the 3-H and H_X protons is observed in the spectrum of 1-vinyl-5-methylpyrazole. The introduction of a methyl group in the 5 position of 1-vinylpyrazole evidently changes the relative orientation of the vinyl group and the pyrazole ring. This leads to a change in the character of the conjugation of the π system of the vinyl group and the heteroring, and this should be reflected in the J_{AB} and δ′ values [8]. For this reason, the J value of the coupling of the ring protons with the methyl protons is also different. It is known that the long-range J coupling constants are stereospecific [8]. A methyl group in the 5 position apparently insures a relative orientation of the 3-H and H_X protons that is suitable for transmission of this coupling.

EXPERIMENTAL

The IR spectra of KBr pellets or microlayers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of CCl_4 solutions were recorded at room temperature with

a B 487B spectrometer with hexamethyldisiloxane as the internal standard (δ scale). Preparative gas–liquid chromatography (GLC) was carried out with a Khrom-3 chromatograph at 170° with a 2.5 m by 10 mm column filled with polyphenyl ether on Chromaton A (0.25-0.315 mm). Activity II aluminum oxide was used for thin-layer chromatography (TLC) with chloroform as the solvent. The pyrazole [9], 3,5-dimethylpyrazole [10], and indazole [11] were obtained by known methods, and the 3(5)-methylpyrazole was the industrial fraction obtained in the Severodonetsk Branch of the State Scientific-Research and Planning Institute of the Nitrogen Industry and Products of Organic Synthesis.

Vinylation of Indazole (I). An autoclave was charged with 30 g of indazole I, 2.4 g (0.01 mole) of cadmium acetate, and 100 ml of dioxane, acetylene was fed into the autoclave at an initial pressure of 17 atm, and the reaction mixture was heated at 180-185° for 2.5 h. The solvent was then removed by distillation, and the residue was vacuum fractionated to give 28 g (80%) of a mixture of 1- and 2-vinylindazoles (V and VI) with bp 104-130° (5 mm) and n_D^{20} 1.6376. Found: C 75.0; H 5.6; N 19.4%. $C_9H_8N_2$. Calculated: C 75.0; H 5.6; N 19.4%. According to the PMR data, the ratio of V and VI was 18:82.

Vinylation of 3(5)-Methylpyrazole. A mixture of 40 g (0.48 mole) of pyrazole III, 2 g (0.002 mole) of CuCl, and 100 ml of dioxane was heated with acetylene at 175-185° for 50 min, after which the vinylation product was separated from the solvent by repeated fractionation to give 41.6 g (79%) of a vinyl fraction with bp 66-86° (30 mm) and n_D^{20} 1.5175. Found: C 66.5; H 7.5; N 26.2%. $C_6H_8N_2$. Calculated: C 66.6; H 7.5; N 25.9%. Fractionation with a rectification column yielded 1-vinyl-3-methylpyrazole (VII) and 1-vinyl-5-methylpyrazole (VIII). In addition to the vinyl fraction, 4.13 g of a mixture of 1,1-bis[3(5)-methyl-1-pyrazolyl]ethane isomers was isolated.

Pyrazoles II and IV were vinylated by a similar method. In addition to the vinyl derivatives, 1-bis(1-pyrazolyl)ethane (XVII), with mp 58° (from heptane) and R_f 0.46, was isolated in the case of pyrazole II when CuCl and $Cd(CH_3COO)_2$ catalysts were used. Found: C 59.2; H 6.2; N 34.9%. $C_8H_{10}N_4$. Calculated: C 59.2; H 6.2; N 34.5%.

In the case of pyrazole IV, 1,1-bis(3,5-dimethyl-1-pyrazolyl)ethane (XVIII), with mp 101° (from heptane) and R_f 0.48, was isolated. Found: C 66.1; H 8.4; N 26.5%. $C_{12}H_{18}N_4$. Calculated: C 66.0; H 8.3; N 26.7%.

1,1-Bis(3,5-dimethyl-1-pyrazolyl)ethane (XVIII). A 0.25-liter autoclave was charged with 1.22 g (0.02 mole) of pyrazole IV, 2.44 g (0.02 mole) of vinylpyrazole X, 0.22 g (0.002 mole) of CuCl, and 40 ml of benzene, and the mixture was heated at 185-190° for 2.5 h. Vacuum fractionation at 120-122° (3 mm) yielded 0.86 g (21%) of a compound with mp 100-101° (from heptane) identical to the compound described above.

1,1-Bis(1-pyrazolyl)ethane (XVII) was similarly synthesized.

Ethylpyrazoles XI-XVI (Table 2). These compounds were obtained by hydrogenation of 1-vinylpyrazoles V-X in ethanol in the presence of Raney nickel.

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DIRECT HYDROXYLATION OF N-SUBSTITUTED [4,5-b]PYRIDINES AND IMIDAZO[4,5-c]PYRIDINES

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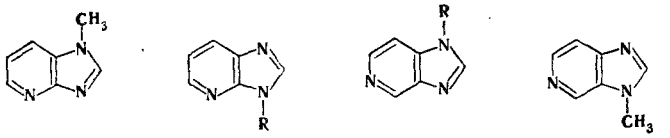
It is shown that when N-methyl (or benzyl) derivatives of imidazo[4,5-b]pyridine and N-methyl-substituted derivatives of imidazo[4,5-c]pyridine are heated with alkalis, the imidazole ring is always hydroxylated to give the corresponding 2-imidazolones.

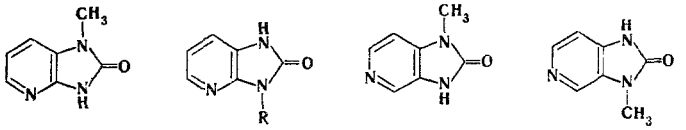
It is known [1, 2] that quinoline and N-alkylbenzimidazoles are readily hydroxylated when they are fused with alkalis. This provides a basis for the assumption that in the case of hydroxylation of N-substituted imidazo[4,5-b]pyridines (I, (II) and imidazo[4,5-c]pyridines (III, IV) the reaction center may be found both in the pyridine and the imidazole fragments of the molecules.



I II a-c III a-c IV

II, III a $R=CH_3$; b $R=CH_2C_6H_5$; c $R=C_6H_5$

When I, IIa,b, IIIa, and IV are heated with excess anhydrous potassium hydroxide to 150-190°C one observes a vigorous reaction with hydrogen evolution to give imidazo[4,5-b]-pyridin-2-ones (V, VIa, b) and imidazo[4,5-c] pyridin-2-ones (VII and VIII) [3].



V VI a, b VII VIII

VI a $R=CH_3$; b $R=CH_2C_6H_5$

The success of this transformation depends decisively on both the mutual orientation of the imidazole and pyridine rings in I-IV and on the nature of the N-substituent. Particularly high yields of imidazopyridin-2-ones are obtained in the imidazo[4,5-b]pyridine series. In this connection one should note that the least basic of the examined compounds (IIa [4]) is hydroxylated under the mildest conditions in almost quantitative yield, whereas this transformation is less characteristic for the more basic imidazo[4,5-c]pyridines (IIIa

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