INDOLE DERIVATIVES

LVIII.* REACTION OF β-(3-INDOLYL)ACRYLALDEHYDE WITH HYDRAZINES

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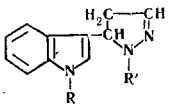
1-Acetyl-5-(3-indolyl)pyrazoline and 1-phenyl-5-(3-indolyl)pyrazoline were obtained by the reaction of β-(1-acetyl-3-indolyl)acrylaldehyde with hydrazine hydrate and phenylhydrazine, respectively, in the presence of acetic acid with subsequent alkaline hydrolysis. The dehydration of the indole derivatives of pyrazoline was studied. α-Bromo-β-(1-acetyl-3-indolyl)acrylaldehyde, which gives 3(5)-(3-indolyl)pyrazole and 1-phenyl-5-(1-acetyl-3-indolyl)pyrazole with hydrazine hydrate in alcohol and phenylhydrazine in acetic acid, respectively, was obtained by the addition of bromine to β-(1-acetyl-3-indolyl)acrylaldehyde and dehydrobromination of the addition product.

We have previously developed a method for obtaining β-(3-indolyl)acrylaldehyde [2]. In this investigation, hydrazone I and azine II were obtained by reaction of this aldehyde with hydrazine hydrate. Compound I is formed only when a 10- to 15-fold excess of hydrazine hydrate is used and is converted to the azine on recrystallization from alcohol. Azine II is readily obtained when the reaction is carried out with an equimolecular amount of hydrazine hydrate in the presence of acids. All attempts to carry out the cyclization of the hydrazone to the pyrazoline in an alkaline medium led to cleavage of the reaction products to indole.

The reaction of β-(1-acetyl-3-indolyl)acrylaldehyde (III) with hydrazine hydrate proceeds similarly, since the acetyl group is cleaved under these conditions. If, however, the reaction is carried out in acetic acid, the azine forms readily. A compound which, from elementary analysis and the IR spectrum is 1-acetyl-5-(1-acetyl-3-indolyl)pyrazoline (IV), was obtained by prolonged refluxing in acetic acid in the presence of excess hydrazine hydrate. In the presence of alkali, IV readily loses one acetyl group and is converted to 1-acetyl-5-(3-indolyl)pyrazoline (V).



IV R = R′ = $COCH_3$
V R = H, R′ = $COCH_3$
VI R = $COCH_3$, R′ = C_6H_5
VII R = H, R′ = C_6H_5

A phenylhydrazone was obtained from β-(3-indolyl)acrylaldehyde and phenylhydrazine; it was cyclized to 1-phenyl-5-(3-indolyl)pyrazoline by refluxing in acetic acid. However, it was chromatographically established that the cyclization does not go to completion even during prolonged refluxing. Under these conditions, the phenylhydrazone of aldehyde III is cyclized more rapidly to give 1-phenyl-5-(1-acetyl-3-indolyl)-pyrazoline (VI) and, after deacetylation, 1-phenyl-5-(3-indolyl)pyrazoline (VII).

Thus nucleophilic 3,4 addition is hindered for β-(3-indolyl)acrylaldehyde; this can be explained by the increased electron density on the β-carbon atom of the side chain due to the electron-donating properties of the indole ring. The introduction of an acetyl group on the heterocyclic nitrogen atom increases the reactivity of this aldehyde with respect to nucleophilic reagents.

*See [1] for Communication LVII.

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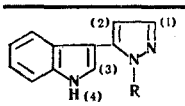
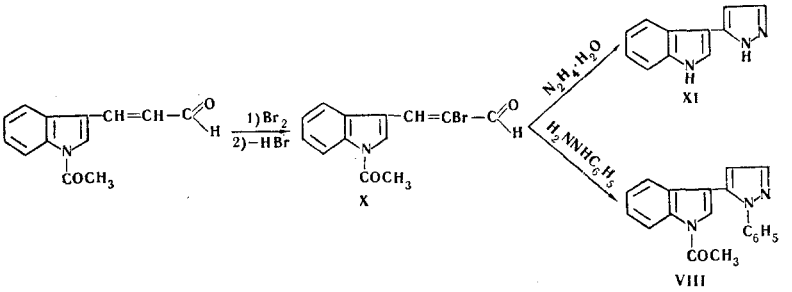
TABLE 1. Chemical Shifts of the Protons and Spin–Spin Constants

	δ_1, ppm	δ_2, ppm	δ_3, ppm	$J_{1,2}$, Hz	$J_{3,4}$, Hz	Solvent
R=C_6H_5	7,75	6,60	6,69	2,0	2,8	$CDCl_2$
R=H	7,61	6,58	7,55	2,0	—	CD_3OD

Dehydrogenation of pyrazoline VI with sulfur [3] gave 1-phenyl-5-(1-acetyl-3-indolyl)pyrazole (VIII) and, after deacetylation, 1-phenyl-5-(3-indolyl)pyrazole (IX).

Dehydrogenation of the other indole derivatives of pyrazoline occurred only at high temperatures (250-280°) and was accompanied by pronounced resinification. α-Bromo-β-(1-acetyl-3-indolyl)acrylaldehyde (X) was therefore obtained for the synthesis of indolylpyrazole by addition of bromine to aldehyde III in acetic acid with subsequent dehydrobromination. 3(5)-(3-Indolyl)pyrazole (XI) and 1-phenyl-5-(1-acetyl-3-indolyl)pyrazole (VIII), which was identical to the compound obtained by dehydrogenation of pyrazoline VI, were obtained from X by reaction with hydrazine hydrate in alcohol and with phenylhydrazine in acetic acid, respectively.



The UV spectrum of 3(5)-(3-indolyl)pyrazole (XI) in alcohol has two maxima, 252 and 288 nm (log ε 4.02 and 3.81). The UV spectrum of 1-phenyl-5-(3-indolyl)pyrazole (IX) has a maximum at 280 nm (log ε 3.99). According to the literature [4], the UV spectrum of pyrazole itself has two maxima at 210 and 250 nm (log ε 3.5 and 1.7). Introduction of substituents that participate in π,π conjugation with the pyrazole ring causes a bathochromic shift of the short-wave band by 25-50 nm [5], which is also observed in the UV spectra of our compounds.

The chemical shifts of the protons and the spin–spin interaction constants in the PMR spectra of the indolylpyrazoles are presented in Table 1.

EXPERIMENTAL

The IR spectra of mineral-oil suspensions were obtained with a UR-10 spectrophotometer. The UV spectra of alcohol solutions were obtained with an SF-4 spectrophotometer. The PMR spectra were recorded with a JNM 4H-100 spectrometer with tetramethylsilane as the internal standard.

Azine of β-(3-Indolyl)acrylaldehyde (II). This was obtained in alcohol in the presence of p-toluenesulfonic acid as the catalyst and had mp 263-264° (from alcohol). Found %: N 16.6, 16.5. $C_{22}H_{18}N_4$. Calculated %: N 16.6. IR spectrum: 3190 (NH), 1610 cm^{-1} (C=C, C=N). UV spectrum: λ_{max} 228, 277, 410 nm (log ε 4.41, 4.17, 4.65).

Hydrazone of β-(3-Indolyl)acrylaldehyde (I). This was obtained in alcohol in the presence of a 10-fold excess of hydrazine hydrate and had mp 140-142°. Found %: N 22.6, 22.4. $C_{11}H_{11}N_3$. Calculated %: N 22.7. IR spectrum: 3320 (NH of the indole ring), 3180 (NH), 1615 cm^{-1} (C=C, C=N). UV spectrum: λ_{max} 226, 282, 328 nm (log ε 4.06, 3.85, 4.20). Azine II with mp 262-264° was obtained after recrystallization from alcohol.

Azine of β-(1-Acetyl-3-indolyl)acrylaldehyde. This was obtained in acetic acid and had mp 276-277°. It was slightly soluble in organic solvents. Found %: N 13.2, 13.4. $C_{26}H_{22}N_4O_2$. Calculated %: N 13.3. IR spectrum: 1715 (C=O), 1625 cm^{-1} (C=C, C=N).

1-Acetyl-5-(1-acetyl-3-indolyl)pyrazoline (IV). Hydrazine hydrate [2 ml (0.04 mole)] and (in portions) 1 g (0.005 mole) of β-(1-acetyl-3-indolyl)acrylaldehyde were added to 20 ml of acetic acid, and the mixture was refluxed for 3 h. It was then cooled, poured into 150 ml of cold water, and the precipitate was filtered to give 0.33 g of IV with mp 211-212° (from toluene). Found %: C 66.7, 66.8; H 6.0, 6.0; N 15.8, 15.9. $C_{15}H_{15}N_3O_2$. Calculated %: C 66.9; H 5.6; N 15.6. IR spectrum: 1715 (C=O), 1650, 1635 cm^{-1} (C=O, C=N). UV spectrum: λ_{max} 270, 310 nm (log ε 4.20, 4.45).

1-Acetyl-5-(3-indolyl)pyrazoline (V). Compound IV (0.5 g) was hydrolyzed with methanolic NaOH to give 0.28 g of V with mp 279-280° (from methanol). Found %: C 68.8; H 5.7; N 18.5, 18.5. $C_{13}H_{13}N_3O$. Calculated %: C 68.7; H 5.8; N 18.5. IR spectrum: 3280 (NH), 1635 (C=O), 1628 cm^{-1} (C=N). UV spectrum: λ_{max} 270, 312 nm (log ε 4.10, 4.37).

Phenylhydrazone of β-(3-Indolyl)acrylaldehyde. This was obtained in alcohol and had mp 162-163° (from dilute alcohol). Found %: C 77.8, 78.1; H 5.7, 5.7; N 16.0, 16.2. $C_{17}H_{15}N_3$. Calculated %: C 78.1; H 5.8; N 16.1. IR spectrum: 3400 (NH of the indole ring), 3315 (NH), 1605 cm^{-1} (C=C, C=N). UV spectrum: λ_{max} 310, 352 nm (log ε 4.17, 4.39).

Phenylhydrazone of β-(1-Acetyl-3-indolyl)acrylaldehyde. This was obtained in alcohol in the presence of a drop of acetic acid and had mp 155-156° (from dilute alcohol). Found %: C 75.5, 75.6; H 5.9, 5.9; N 13.9, 14.0. $C_{19}H_{17}N_3O$. Calculated %: C 75.2; H 5.6; N 13.8. UV spectrum: λ_{max} 302, 376 nm (log ε 4.20, 4.56).

1-Phenyl-5-(1-acetyl-3-indolyl)pyrazoline (VI). A. β-(1-Acetyl-3-indolyl)acrylaldehyde [2.1 g (0.01 mole)] was stirred with 20 ml of acetic acid, 1.1 ml of phenylhydrazine was added, and the mixture was stirred until a voluminous precipitate formed, after which it was heated to boiling and refluxed for 30 min. The acetic acid was removed, and the residue was diluted with water and neutralized with bicarbonate. The resulting precipitate was recrystallized from alcohol to give 2.1 g (70%) of VI with mp 164-165°. Found %: C 75.2, 75.2; H 5.8, 6.0; N 13.5, 13.8. $C_{19}H_{17}N_3O$. Calculated %: C 75.2; H 5.6; N 13.8. IR spectrum: λ_{max} 238, 270 nm (log ε 4.8, 4.22).

B. β-(1-Acetyl-3-indolyl)acrylaldehyde phenylhydrazone (0.65 g) was added to 20 ml of acetic acid, and the mixture was refluxed for 30 min. Treatment of this mixture in accordance with method A gave 0.45 g of VI with mp 163-164° (from alcohol).

1-Phenyl-5-(3-indolyl)pyrazoline (VII). Pyrazoline VI (0.5 g) was hydrolyzed by heating with aqueous methanolic NaOH. After recrystallization from benzene–heptane, 0.3 g of VII with mp 133-134° was obtained. Found %: C 78.5, 78.4; H 6.0, 6.1; N 16.2, 16.0. $C_{17}H_{15}N_3$. Calculated %: C 78.1; H 5.8; N 16.1. IR spectrum: 3440 (NH), 1600 cm^{-1} (C=N). UV spectrum: λ_{max} 282, 290 nm (log ε 4.20, 4.16).

α-Bromo-β-(1-acetyl-3-indolyl)acrylaldehyde (X). A solution of 8 g (0.05 mole) of bromine in 20 ml of acetic acid was added dropwise with stirring to a mixture of 80 ml of acetic acid and 10 g (0.047 mole) of β-(1-acetyl-3-indolyl)acrylaldehyde. The mixture was stirred for 15 min, and 8 g of pulverized anhydrous potassium carbonate was added carefully. The mixture was slowly heated to the boiling point, cooled, and poured into 500 ml of cold water. The precipitate was washed with water and recrystallized from tetrahydrofuran to give 7.6 g (55%) of X with mp 234°. Found %: C 53.7; H 3.3; Br 27.4; N 4.7. $C_{13}H_{10}BrNO_2$. Calculated %: C 53.5; H 3.5; Br 27.4; N 4.8. IR spectrum: 1733, 1688 (C=O); 1670 cm^{-1} (C=C). UV spectrum: λ_{max} 384 nm (log ε 4.57).

1-Phenyl-5-(1-acetyl-3-indolyl)pyrazole (VIII). A. Pyrazoline VI [1.05 g (0.0035 mole)] was mixed with 0.16 g of sulfur, and the mixture was heated at 170-180° until hydrogen sulfide evolution ceased. After recrystallization from benzene, 0.6 g (60%) of VIII with mp 197-198° was obtained. Found %: C 75.8; 75.7; H 5.0, 5.0; N 13.8, 14.0. $C_{19}H_{15}N_3O$. Calculated %: C 75.7; H 5.0; N 13.9. IR spectrum: 1710 cm^{-1} (C=O). UV spectrum: λ_{max} 302 nm (log ε 4.00).

B. A mixture of 20 ml of acetic acid, 0.5 g (0.0017 mole) of X, and 0.2 ml (0.002 mole) of phenylhydrazine was refluxed for 1 h. The acetic acid was removed by distillation, and the residue was washed with water and recrystallized from benzene–heptane to give 0.23 g (57%) of VIII with mp 196-198°.

1-Phenyl-5-(3-indolyl)pyrazole (IX). Pyrazole VIII (0.5 g) was hydrolyzed in an aqueous alcoholic NaOH to give 0.3 g (70%) of IX with mp 110-112° (from benzene–heptane). Found %: C 79.0; H 5.3; N 16.4. $C_{17}H_{13}N_3$. Calculated %: C 78.8; H 5.0; N 16.2. IR spectrum (CCl_4): 3500 cm^{-1} (NH). UV spectrum: λ_{max} 280 nm (log ε 3.99).

3(5)-(3-Indolyl)pyrazole (XI). Aldehyde X [0.73 g (0.0025 mole)] was added in small portions to a solution of 2.5 ml (0.05 mole) of hydrazine hydrate in 20 ml of isopropyl alcohol, and the mixture was refluxed for 1 h. It was then cooled and poured into 100 ml of water. The resulting mixture was extracted with ether. The ether was removed after drying the extract with potassium carbonate, and the residue was recrystallized to give 0.27 g (60%) of XI with mp 159-160° (from benzene). Found %: C 72.3; 72.1; H 5.3, 5.2; N 22.8, 22.6. $C_{11}H_9N_3$. Calculated %: C 72.1; H 4.9; N 22.9. IR spectrum: 3320 (NH), 3200 cm^{-1} (NH). UV spectrum: λ_{max} 252, 282, 288 nm (log ε 4.02, 3.81, 3.81). The hydrochloride had mp 216-218° (decomp., reprecipitated from absolute alcohol with ether). Found %: C 60.2, 60.3; H 4.7, 4.6; Cl 16.1, 16.3; N 18.8, 19.0. $C_{11}H_9N_3 \cdot HCl$. Calculated %: C 60.1; H 4.6; Cl 16.1; N 19.1. IR spectrum: 3320, 3140 (NH), 2580-2800 cm^{-1} (N^+-H).

LITERATURE CITED

1. Yu. I. Smushkevich, N. N. Mar'yanovskaya, and N. N. Suvorov, Trudy MKhTI im. Mendeleeva, 61, 154 (1969).
2. N. N. Suvorov, V. P. Gorbunova, and K. F. Turchin, Khim. Geterotsikl. Soedin., 1029 (1968).
3. I. I. Grandberg and A. N. Kost, Zh. Obshch. Khim., 28, 3017 (1958).
4. I. I. Grandberg, Zh. Obshch. Khim., 33, 519 (1963).
5. I. I. Grandberg and A. N. Kost, Zh. Obshch. Khim., 32, 3025 (1962).