SYNTHESIS OF 3-(2-PYRROLYL)INDOLES

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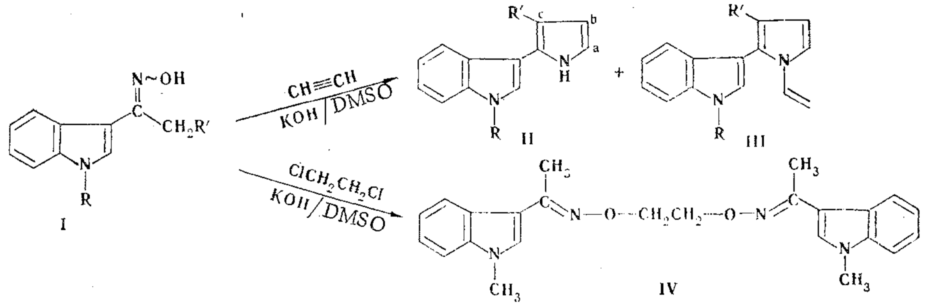
New 3-(2-pyrrolyl)indole systems were synthesized on the basis of heterocyclization of 3-acylindole oximes with acetylene in a superbase medium (the Trofimov reaction). It is shown that only the anti form of the oxime participates in the formation of the pyrrole ring.

A fundamentally new method for the synthesis of a pyrrole ring, which consists in the reaction of ketone oximes with acetylene in superbase media (the Trofimov reaction), has been recently developed [1]. Thus far the subjects of the investigation of this reaction have been primarily oximes of aliphatic and aliphatic aromatic ketones and only two representatives of oximes of ketones of the heterocyclic series, viz., acylbenzothiazoles and acetylbenzimidazole. 3-Acylindole oximes have not been used in this reaction, although the combination of indole and pyrrole rings may be of interest from a pharmacological point of view.

The present research was devoted to the synthesis of 3-(2-pyrrolyl)indoles by the indicated method. 1-Methyl-3-acetylindole oximes (I) were selected as models for heterocyclization under the influence of acetylene in a superbase medium.



The reactions of 1-methyl-3-acylindole oximes (Ia,c,e) with acetylene lead to pyrrolylindoles II in 40-45% yields. N-Vinylpyrrolylindoles III are formed as side products (in 10-20% yields). This reaction is very sensitive to the conditions under which it is carried out. The ratios of reaction products II and III change as a function of the medium and the reaction temperature and time. The character of the superbase medium plays the principal role in this case. It is known from the literature [1, 2] that the catalytic activity of the superbase pair (strong base—DMSO) depends on the nature of the cation, and peak activity is observed for potassium; we therefore selected potassium hydroxide as the base. The ketoxime:KOH ratio has a great effect on the ratio of the products of the principal and side reactions. A change in this ratio from 1:10 to 1:1.2 led to a 15% decrease in the yield of N-vinylated III and a 15% increase in the yield of the pyrrolylindole. This is explained by the fact that the decrease in the rate of vinylation at the pyrrole nitrogen atom as the ketoxime:KOH ratio is decreased is more significant than the decrease in the rate of formation of the pyrrole. The same effect is also observed when the temperature is decreased. In addition, virtually no resinification occurs at lower temperatures, and it was therefore found that the optimum reaction temperature is 100-105°C (a pyrrole is not formed at lower temperatures). The reaction time plays a substantial role in the change in the yields of pyrrolylindoles II. The passage of acetylene into the reaction mixture is discontinued when the amount of pyrrolylindole no longer increases [according to data from thin-layer chromatography (TLC)], and the amount of the side vinylation product begins to increase (in different cases the reaction time ranged from 0.5 h to 1.5-2 h).

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TABLE 1. 3-(2-Pyrrolyl)indoles

Compound	R	R'	mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
				C	H		C	H	
IIa	CH_3	H	108—110	79,6	6,3	$C_{13}H_{12}N_2$	79,6	6,1	35
IIb	H	CH_3	168—169	80,1	7,2	$C_{13}H_{12}N_2$	79,6	6,1	32
IIc	CH_3	CH_3	153—155	80,0	6,8	$C_{14}H_{14}N_2$	80,0	6,7	44
IId	H	*iso*-C_3H_7	115—117	80,3	7,3	$C_{15}H_{16}N_2$	80,4	7,1	35
IIe	CH_3	*iso*-C_3H_7	102—104	80,6	7,8	$C_{16}H_{18}N_2$	80,7	7,6	41

TABLE 2. Spectral Characteristics of 3-(2-Pyrrolyl)indoles

Compound	IR spectrum, cm^{-1} (N—H)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm				
			2-H	4-H	a-H	b-H	c-H
IIa	3380	212 (4,19), 245 (4,30), 320 (3,72)	7,36	7,95	6,26	6,80	6,46
IIc	3350	212 (4,27), 242 (4,33), 305 (3,65)	7,30	7,68	6,00	6,70	—
IIe	3370	213 (4,29), 240 (4,33), 300 (3,66)	7,23	7,61	6,13	6,80	—
IIb	3350	212 (4,24), 240 (4,26), 300 (3,62)	7,26	7,75	6,03	6,76	—
IId	3375	213 (4,27), 240 (4,30), 300 (3,63)	7,30	7,58	6,13	6,83	—

A band corresponding to the stretching vibrations of the N—H group at 3350 cm^{-1} appears in the IR spectra of the synthesized pyrrolylindoles II, and this indicates the formation of a pyrrole ring.

Characteristic multiplet signals of pyrrole ring protons appear in the PMR spectra of II at 6 to 7 ppm [3]. For example, signals of pyrrole a-H, b-H, and c-H pyrrole protons are found at 6.26, 6.80, and 6.46 ppm, respectively, in the PMR spectrum of 1-methyl-3-(2-pyrrolyl)-indole (IIa). A singlet signal of protons of a methyl group attached to the indole nitrogen atom is found in the strong-field region (at 3.80 ppm).

A shift of the signals of the 2-H and 4-H protons to the strong-field region is observed in the PMR spectra on passing from 3-acylindole oximes [4] to pyrrolylindoles (Table 2). For example, the signal of the 2-H proton is shifted from 7.58 ppm to 7.36 ppm and the signal of the 4-H proton is shifted to 8.35 ppm to 7.95 ppm on passing from 1-methyl-3-acetylindole oxime to pyrrolylindole IIa. While the change in the chemical shift of the signal of the 2-H proton is satisfactorily explained by electronic factors [replacement of the acceptor oxime function in the 3 position of the indole ring by the more pronounced (as compared with it) donor pyrrole function leads to a change in the electron density on the α-carbon atom], the shift of the signal of the 4-H proton can evidently be explained by a change in the anisotropy of the substituent in the 3 position.

In the UV spectrum of 1-methyl-3-(2-pyrrolyl)indole (IIa) the long-wave absorption band [λ_{max} 317 nm (log 3.46)] experiences a bathochromic shift as compared with the analogous band of indole [λ_{max} 288 nm (log ε 3.69)]. When alkyl substituents are present in the 3 position of the pyrrole ring, one observes a small hypsochromic shift of this long-wave band (R' = H, λ_{max} 317; R' = CH_3, λ_{max} 305; R' = $CH(CH_3)_2$, λ_{max} 300 nm); this may constitute evidence for a certain degree of disruption of the planarity of the system.

The character of the mass-spectral fragmentation of pyrrolylindoles II completely confirms the proposed structure. Thus the most intense peak in the mass spectrum of pyrrolylindole IIa (R' = H) is the molecular-ion peak M^+ 196.* The principal fragmentation pathways are elimination of HCN from both the molecular ion and from the fragment ions; another fragmentation pathway is splitting out of the methyl group attached to the indole nitrogen atom.

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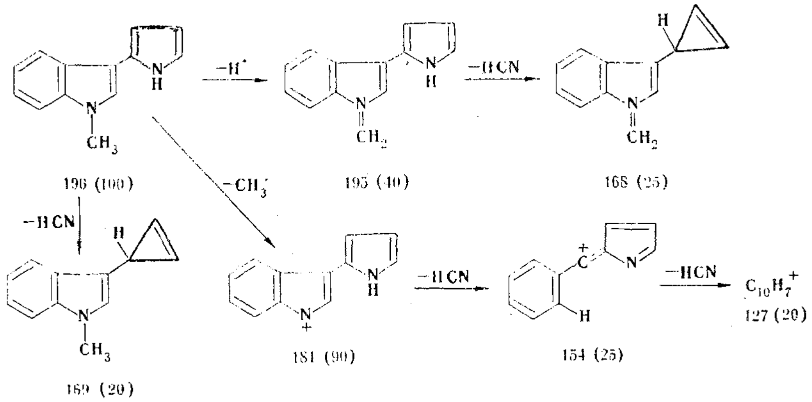
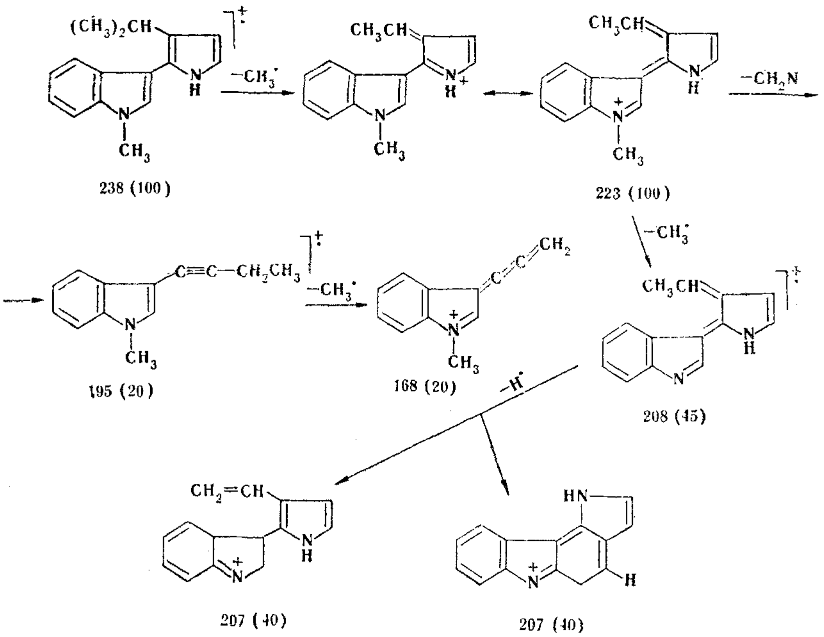
*Here and subsequently, the m/z values are given for the ion peaks, and the relative intensities in percent of the maximum peak are given in parentheses.



Fragmentation is complicated somewhat when there is a substituent in the 3 position of the pyrrole ring, and this substituent participates in it. Thus, for example, the fragmentation of 1-methyl-3-(3-isopropyl-2-pyrrolyl)indole (IIe) can be represented by the scheme:*



Thus we have shown that the reaction of 1-methyl-3-acylindole oximes with free acetylene leads to the formation of 3-(2-pyrrolyl)indoles.

If dichloroethane (DCE) is used instead of acetylene for the heterocyclization of oximes I in a superbase medium at an oxime:DCE:KOH:DMSO molar ratio of 1:(1-2):7:10, the product at 115°C is not a pyrrole but rather bisether oxime IV, which is formed due to nucleophilic substitution of the halogen in dichloroethane by the oximate anion.

The PMR spectrum of bisether IV in trifluoroacetic acid gives a ratio of the integral intensities of the aliphatic and aromatic protons of 16:10 (8:5), which made it possible to assume the existence of a bisether structure. The molecular mass of IV is 402 on the basis of the mass-spectral data. The most intense peak in the mass spectrum corresponds to the $[M-C_2H_4]^+$ ion with m/z 187.

The oxime O-anion that is readily formed in the KOH—DMSO medium probably nucleophilically attacks the dichloroethane molecule more rapidly than the rate at which the acetylene that is necessary for the formation of a pyrrole ring is formed. A decrease in the rate of addition of the dichloroethane led to the formation of a very small amount of the pyrrolylindole, but the principal product was still bisether IV. The formation of a bisether with a similar structure in the aliphatic ketoxime series was independently observed in [5] when the "dichloroethane" method was used.

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Just as in the case of N-methylated derivatives, the reaction of N-unsubstituted 3-acylindole oximes (Ib,d) with free acetylene in a superbase medium led to the formation of pyrrolylindoles IIb,d, but in this case the reaction is complicated by vinylation of not only the pyrrole nitrogen atom but also the indole nitrogen atom, which leads to a decrease in the yields of pyrrolylindoles to 30-35% (Table 1).

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Perkin-Elmer 402 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with UR-20 and Perkin-Elmer 557 spectrometers. The PMR spectra of solutions in d_6-acetone were obtained with T-60 and Varian XL-100 spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-112 spectrometer at an ionizing voltage of 70 eV. Chromatographic purification of the pyrrolylindoles was carried out with a column packed with neutral activity II Al_2O_3 (Brockmann scale) in a stream of argon by elution with benzene—pentane (1:1). The course of the reactions and the purity of the substances were monitored by means of TLC on Silufol UV-254 in a benzene—ethyl acetate system (5:1).

3-(2-Pyrrolyl)indoles (IIa-e). Acetylene (previously purified with sulfuric acid and dried with solid KOH) was passed with continuous stirring through a mixture of 0.005 mole of oxime I, 0.006 mole of KOH, 20 ml of DMSO, and 0.5 ml of water heated to 105-110°C. The reaction was carried out for 0.5-1.5 h. The course of the reaction was monitored by means of TLC. At the end of the reaction the reaction mixture was poured over ice, and the aqueous mixture was extracted with benzene. The benzene extract was washed with water and dried with Na_2SO_4, and the solvent was removed by vacuum distillation. The residue was chromatographed with a column. Data on pyrrolylindoles II are presented in Table 1.

1,2-Bis[1-(1-methyl-3-indolyl)ethylidene-1-iminoxy]ethane (IV). A solution of dichloroethane in DMSO (1:1) was added in portions (five to six 1.3-ml portions) in the course of 3 h at 115°C to a mixture of 0.005 mole of oxime Ib, 0.005 mole of KOH, and 9 ml of DMSO. A 0.15-g sample of KOH was added prior to the addition of each portion. According to the data from TLC on Silufol [benzene—methyl ethyl ketone (20:1)], the starting oxime did not react completely in this amount of time, and another 2 ml of dichloroethane was therefore added, and the mixture was heated for 30 min. The cooled reaction mixture was poured into ice water, and the aqueous mixture was extracted with ether. The extract was dried with Na_2SO_4, and the solvent was evaporated. The residue was chromatographed with a column packed with silica gel (100/160 μ) in benzene to give bisether IV, with mp 163-165°C, in 35% yield. Found: C 71.7; H 6.7%; M^+ 402. $C_{24}H_{26}N_4O_2$. Calculated: C 71.6; H 6.5%; M 402.

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