INDOLE DERIVATIVES.

129.* REACTION OF 5-VINYLINDOLE WITH BROMINATING AGENTS

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The bromination of 5-vinylindole at two reaction centers, viz., the carbon—carbon multiple bond of the vinyl group and the pyrrole ring, was realized. In the case of the reaction with pyridinium bromide perbromide it was shown that the pyrrole ring is the most reactive with respect to electrophilic agents. It was established that the introduction of an electron-acceptor acetyl group into the pyrrole ring leads to a decrease in the reactivity of the pyrrole ring, and bromination takes place at the double bond.

5-Vinylindole, which we recently obtained [2], is a promising intermediate for the synthesis of new indole derivatives. Unfortunately, the literature contains an extremely limited amount of information regarding the reactivities of such compounds, particularly regarding their reactions with halogenating agents [3-9]. The available data indicate the complex character of this process. It has been shown [3, 4], for example, that the reaction of 1-vinylindole with hydrogen halides leads to the formation of polymeric charge-transfer complexes. In the reaction of 9-vinylcarbazole with bromine and several other halogenating agents addition to the multiple bond of the vinyl group is accompanied by electrophilic substitution in the aromatic system [5]. The process is also complicated by the fact that indole and compounds similar to it react readily with halogens with the formation of oxidation and electrophilic-substitution products [6-9].

The peculiarity of the properties of vinyl derivatives of the pyrrole series is associated with the presence of two nucleophilic centers, viz., the multiple bond of the vinyl group and the pyrrole ring. Taking this into account, we studied the reaction of 5-vinylindole with brominating agents under the conditions of competing reactions, viz., substitution in the pyrrole ring and addition to the carbon—carbon multiple bond of the vinyl group.

We used a solution of bromine in carbon tetrachloride, pyridinium bromide perbromide, dioxane dibromide, and N-bromosuccinimide as the brominating agents.

The reaction of 5-vinylindole (Ia) with bromine in carbon tetrachloride at —20°C leads to the formation of an insoluble (in ordinary solvents) dark colored substance with a decomposition temperature of ~300°C, the empirical formula of which ($C_{10}H_{11}BrN$) attests to the presence of one bromine atom in the indole molecule. The IR spectrum does not contain a band of stretching vibrations of a C=C bond at 1600 cm^{-1}. The presence of a band of stretching vibrations of the NH bond of a pyrrole ring at 3440 cm^{-1} and of a band at 740 cm^{-1} (deformation vibrations of the $-CH_2-$ group of a polymer chain) makes it possible to assume that the compound obtained is a polymer of 3-bromo-5-vinyl-indole.

When pyridinium bromide perbromide is used as the brominating agent, the principal reaction product (according to data from the PMR spectra of the carbon tetrachloride extract of the reaction mixture; Table 1) is 3-bromo-5-vinylindole (IIa).

The formation of 3-bromo-5-vinylindole under these conditions is not unexpected, since indole forms 3-bromoindole with pyridinium bromide perbromide under similar conditions [8]. The fact that signals of protons of a 1,2-dibromethyl group are not observed in the PMR spectrum is interesting. This indicates the absence of any appreciable amounts of 5-(1,2-dibromoethyl)indole, although it is known that pyridinium bromide perbromide is a selective

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*See [1] for communication 128.

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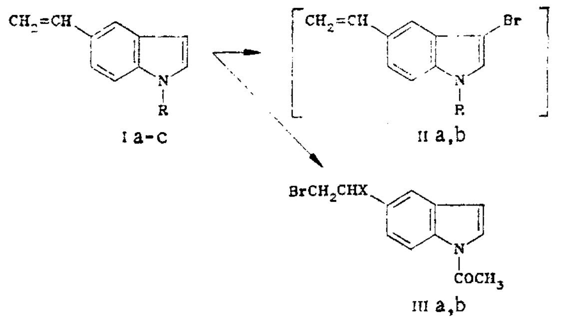

I a R=H, b R=CH_3, c R=$COCH_3$; II a R=H, b R=CH_3, III a X=Br, b X=OH

brominating agent in reactions involving electrophilic addition to the double bond [10]. Unfortunately, we were unable to isolate 3-bromo-5-vinylindole from the reaction mass, since, when the concentration of the solution is increased, it is converted, as a consequence of polymerization, to an infusible insoluble substance with a decomposition temperature of ~300°C, which is similar to the compound obtained by the action of bromine in carbon tetrachloride on 5-vinylindole.

The bromination of 1-methyl-5-vinylindole (Ib) under similar conditions leads, according to the PMR spectral data (the absence of signals of protons in the 3 position), to the formation of 1-methyl-3-bromo-5-vinylindole (IIb); the double bond is not affected in this case also.

Thus a 3-bromo derivative with retention of the vinyl group is formed in the bromination of 5-vinylindole, as well as in the bromination of 1-methyl-5-vinylindole; this constitutes evidence for the higher reactivity of the pyrrole ring with respect to these electrophilic agents.

It is known that the introduction of an electron-acceptor group at the nitrogen atom leads to a decrease in the reactivity of the pyrrole ring. In fact, in the reaction of 1-acetyl-5-vinyl-indole (Ic), which was obtained by acylation of 5-vinylindole, with pyridinium bromide perbromide bromine adds to the double bond of the vinyl group. The resulting 1-acetyl-5-(1,2-dibromoethyl)indole (IIIa) was isolated in 26% yield. A band of stretching vibrations of a carbonyl group (1750 cm^{-1}) is observed in its IR spectrum, but bands at 1630 and 990 cm^{-1} corresponding to the vibrations of a vinyl group are absent. Signals of the protons of a dibromoethyl group at 4.26 and 4.29 ppm (nonequivalent protons of the CH_2 group) and at 5.5 ppm (CH) and signals of 2-H and 3-H protons of the indole ring at 7.78 and 6.68 ppm are observed in the PMR spectrum; as a consequence of the anisotropic effect of the N-acetyl group, the signal of the 7-H proton is shifted to the weak-field region and shows up at 8.36 ppm.

The same substance is formed in the reaction of 1-acetyl-5-vinylindole with other brominating agents, particularly with bromine in carbon tetrachloride and with dioxane dibromide in 10% and 7% yields, respectively. The formation of a 1,2-dibromoethyl derivative when there is an acetyl group attached to the nitrogen atom of the pyrrole ring indicates a decrease in the reactivity of the pyrrole ring.

The data on the bromination of 5-vinylindole obtained in this research indicate the possibility of the selective bromination at the two reaction centers; this opens up extensive possibilities for the synthesis of new difficult-to-obtain indole derivatives that are substituted in the benzene part of the molecule. In particular, we were able to synthesize 5-vinylindole bromohydrin (IIIb) by the action of bromine on 1-acetyl-5-vinylindole (Ic) in an aqueous medium. The reaction with 1-acetyl-5-vinylindole (Ic) was carried out in dimethyl sulfoxide (DMSO) with the addition of water in a stream of nitrogen. N-Bromosuccinimide was used as the brominating agent. Bands of stretching vibrations of carbonyl (1720 cm^{-1}) and hydroxy (3590 cm^{-1}) groups are observed in the IR spectrum of bromohydrin IIIb. The PMR spectrum contains signals of protons of the $CH_2BrCHOH$ fragment at 3.62 and 3.60 ppm (nonequivalent protons of the CH_2 group), 5.01 ppm (CH), and 4.25 ppm (OH). The realization of precisely this isomer is confirmed by low-temperature studies of the PMR spectra: slowing down of exchange of the hydroxy protons below −50°C leads to broadening of the doublet–doublet lines of the CH signal as a consequence of the development of a constant of spin–spin coupling between the CH and OH protons.

TABLE 1. PMR Spectra of 5-Vinylindoles Ib, c and Their Bromination Products II and III in d_6-Acetone

Compound	Chemical shifts, δ, ppm											SSCC, Hz					
	1-H	2-H	3-H	4-H	6-H	7-H	CH_3	a-H	b-H	c-H	OH	J_{12}	J_{23}	J_{67}	J_{bc}	J_{ab}	J_{ac}
Ib	—	7,12	6,32	7,54	7,29		3,76	6,79	5,03	5,64			3,2		1,4	19,9	17,6
Ic	—	7,42	6,63	7,60	7,43	8,29	2,77	6,85	5,16	5,79			3,0	8,8	1,0	11,0	17,3
IIa	7,9	7,03	—	7,44	7,24	7,10	—	6,75	5,08	5,65	—	2,6	—		1,0	10,8	17,5
IIIa	—	7,78	6,68	7,46	7,74	8,36	2,89	5,5	4,26	4,29	—	—	3,8			6,5	8,9
IIIb	—	7.43	6.62	7.59	7.31	8.39	2.62	5.01	3.62	3.60	4.25		3.5	8.5	10.3	3.7	8.6

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were obtained with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a WP-200-SY spectrometer with tetramethylsilane (TMS) as the internal standard.

The characteristics of the compounds obtained are presented in Table 1.

5-Vinylindole was obtained by the method in [2].

1-Methyl-5-vinylindole (Ib). A 2-g (14 mmole) sample of 5-vinylindole and 6.5 ml (80 mmole) of 50% sodium hydroxide solution were added to a mixture of 3.1 ml (20 mmole) of methyl iodide and 0.027 g (0.16 mmole) of trimethylbenzylammonium chloride, after which the temperature was raised to 70°C with vigorous stirring, and the mixture was maintained under these conditions for 6 h. It was then cooled and diluted with 25 ml of water, and the resulting oil was extracted with ether. The ether extracts were dried with magnesium sulfate and evaporated, and the resulting oil was distilled in vacuo to give 1.1 g (50%) of a product with bp 150-155°C (10 hPa) and n_D^{20} 1.6245. Found, %: C 84.4, H 7.3, N 8.9. $C_{11}H_{11}N$. Calculated, %: C 84.05, H 7.05, N 8.9.

1-Acetyl-5-vinylindole (Ic). A 1.1-g (30 mmole) sample of powdered sodium hydroxide and, dropwise, a solution of 1.2 g (10 mmole) of acetyl chloride in 10 ml of methylene chloride were added to a solution of 1.5 g (10 mmole) of 5-vinylindole and 0.042 g (0.25 mmole) of trimethylbenzylammonium chloride in 32 ml of dried (over P_2O_5) methylene chloride. At the end of the addition of the acetyl chloride, the reaction mass was refluxed for 1.5-2 h, and the solution was cooled and filtered. The filtrate was evaporated, and the residue was recrystallized from hexane to give 1.8 g (93%) of colorless crystals with mp 71°C. IR spectrum: 1700 (C=O), 1630 cm^{-1} (C=C). Found, %: C 77.8, H 6.0, N 7.6. $C_{12}H_{11}NO$. Calculated, %: C 78.2, H 78.2, H 6.1, N 7.5.

Reaction of 5-Vinylindole with Bromine in Carbon Tetrachloride. A solution of 0.15 g (1 mmole) of 5-vinylindole in 4 ml of carbon tetrachloride was cooled to −20°C, and a solution of 0.2 g (1.25 mmole) of bromine in 2 ml of carbon tetrachloride was added dropwise, during which a yellow precipitate, which darkened rapidly at 20°C, formed. The precipitate was removed by filtration, washed with 15 ml of CCl_4 (three 5-ml portions), and dried to give 0.3 g of a product with T_{dec} 250-300°C. IR spectrum: 3440 (NH), 740 cm^{-1} (CH_2).

Reaction of 5-Vinylindole with Pyridinium Bromide Perbromide. A solution of 0.2 g (1.4 mmole) of 5-vinylindole in 2 ml of pyridine was cooled to −15°C, and a solution of 0.54 g (1.7 mmole) of pyridinium bromide perbromide in 1.5 ml of pyridine was added with stirring in the course of 30 min. At the end of the addition, the mixture was stirred at −15°C for another 30 min and then poured into 30 ml of cold CCl_4. The mixture was filtered to remove the precipitated pyridine salts, and the filtrate was washed successively with 30 ml of cold 5% hydrochloric acid and water until the wash water was neutral and then dried with $MgSO_4$. For PMR spectroscopic investigation the solution was evaporated without heating to a volume of 5-10 ml. The formation of a yellowish oil, which subsequently at 0°C in a few minutes was converted to an insoluble substance with T_{dec} 250°C, was observed when the concentration was increased further. The same compound began to precipitate from the solution after a few hours. IR spectrum: 3440 (NH), 740 cm^{-1} (CH_2).

1-Acetyl-5-(1,2-dibromoethyl)indole (IIIa). A) A solution of 0.45 g (1.4 mmole) of pyridinium bromide perbromide in 1.5 ml of pyridine was added dropwise with stirring to a solution of 0.2 g (1.1 mmole) of 1-acetyl-5-vinylindole in 2 ml of pyridine cooled to −15°C. At the end of the addition of the entire solution, the reaction mass was stirred for another 30 min and then poured into 50 ml of cold ether. The mixture was filtered to remove the precipitate, and the filtrate was washed successively with dilute hydrochloric acid solution and water until the wash water was neutral. The ether solution was dried with magnesium sulfate and evaporated. Fractional crystallization of the resulting oil from petroleum ether yielded 0.07 g (26%) of 1-acetyl-5-(1,2-dibromoethyl)indole in the form of colorless crystals with mp 97-99°C. IR spectrum: 1750 cm^{-1} (C═O). UV spectrum (in ethanol), λ_{max} (log ε): 205 (3.28), 243 (3.47), 274 (2.97), 292 (2.74), 302 nm (2,74). Found, %: C 42.2, H 3.2, Br 46.7, N 4.1. $C_{12}H_{11}Br_2NO$. Calculated, %: C 41.8, H 3.2, Br 46.3, N 4.06.

B) A solution of 0.2 g (1.25 mmole) of bromine in 2 ml of CCl_4 was added in small portions to a solution of 0.2 g (1.1 mmole) of 1-acetyl-5-vinylindole in 4 ml of CCl_4 cooled to −20°C, and the resulting solution was washed with water, dried with magnesium sulfate, and evaporated. The residue was worked up as in experiment A to give 0.4 g (10%) of a product with mp 99°C.

C) A solution of 0.2 g (1.1 mmole) of 1-acetyl-5-vinyl-indole in 5 ml of ether was cooled to −25°C, and 0.4 g (1.6 mmole) of dioxane dibromide was added in small portions. The mixture was then worked up as in experiment A to give 0.028 g (7%) of a product with mp 98°C.

1-Acetyl-5-(1-hydroxy-2-bromoethyl)indole (IIIb). A mixture of 1 g (5.5 mmole) of 1-acetyl-5-vinylindole, 20 ml of dimethyl sulfoxide (DMSO), and 0.1 ml (5.5 mmole) of water was cooled to 10°C, and 1.1 g (6 mmole) of N-bromosuccinimide was added all at once in a stream of argon. Analysis by thin-layer chromatography (TLC) was carried out. At the end of the reaction, the mixture was poured into water, and the resulting oil was extracted with benzene. The extract was washed with water to remove the DMSO, dried with magnesium sulfate, and evaporated. Two spots, viz., the starting 1-acetyl-5-vinylindole and 1-acetyl-5-(1-hydroxy-2-bromoethyl)indole, were observed on the chromatogram. The latter was isolated with a column (300 × 15 mm) packed with L 100/250 silica gel suspended in ethyl acetate–petroleum ether (1:4), which was used as the eluent. Recrystallization from petroleum ether gave 0.8 g (50%) of 1-acetyl-5-(1-hydroxy-2-bromoethyl)indole in the form of white crystals with mp 88-90°C. IR spectrum (in methylene chloride): 1720 (C═O), 3590 cm^{-1} (OH). Found, %: C 50.8, H 4.41, Br 28.5, N 5.16. $C_{12}H_{12}BrNO_2$. Calculated, %: C 51.1, H 4.3, Br 28.4, N 4.96.

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