SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1-(α-ALKOXYETHYL) INDOLES

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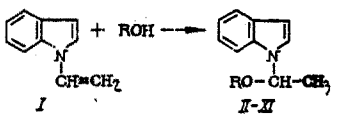
By introducing various alcoholic residues into the molecule of 1-vinylindole (I), its biological activity can be modified [1]. We carried out the search for new compounds with antimicrobial activity by regulating the length and structure of the aliphatic chain of the alkoxy substituent of indole.

In this connection, in the present work we continued the study of the addition reaction of alcohols to 1-vinylindole. We have already proposed [2] a catalyst, consisting of a mixture of acetic and boric acids and copper acetate in a ratio of 6:1:2. The investigation carried out in the present work confirmed that the use of this three component catalyst does in fact favor active electrophilic addition of more complex alcohols to the double bond of the vinyl group in 1-vinylindole and suppresses the competing polymerization reaction. In this case, the synthesis of new 1-(α-alkoxyethyl)indoles III-XI proceeds to high yield (up to 80%). We were able to add to the double bond of vinylindole not only butyl, amyl, hexyl, and heptyl alcohols, but also cyclohexanol, benzyl, and allyl alcohols.



I II-XI

R = C_nH_{2n+1} (n = 1, 4-7), C_6H_{11}, $C_6H_5CH_2$, C_3H_5

An attempt to simplify the composition of the catalyst failed. Thus, in the presence of copper acetate, the reaction with alcohols generally does not take place, and the initial I is isolated from the reaction mixture. Exclusion of copper acetate from the catalytic system leads to decrease in the yield of the desired products and increase in resinification.

The optimal conditions for the reaction studied is the reaction of I with alcohols at 105-120°C for 2 h 30 min in the presence of the catalyst. It was found that primary alcohols add most easily. For example, the yield of alkoxyethylindoles III, IV, VII reaches 73-77%, while sec-butyl alcohol reacts with great difficulty with vinyl indole, and tert-butyl alcohol cannot add to I. The reaction with allyl alcohol requires rigid control of temperature conditions (98-102°C). An increase in temperature to 120°C causes polymerization of the reaction mixture; with a decrease in temperature to 15-20°C, the reaction does not proceed. The new alkoxyethylindoles (III-XI) that we synthesized are high-boiling, oily, colorless liquids with a specific weight close to unity. They are soluble in most organic solvents. The physicochemical constants and data of elemental analysis are listed in Table 1. If we compare the IR spectra of I with those of the products of its reaction with alcohols, we observe the disappearance in the latter of the absorption band at 1643 cm^{-1}, characteristic of the vinyl group of I. In the IR spectra of compounds III-XI, absorption is observed in the region of 1100-1120 cm^{-1} characteristic of the C–O–C bond, in the 1378-1380 cm^{-1} region corresponding to the vibrations of the methyl group of alkoxyethylindoles, and several bands in the 2870-2990 cm^{-1} region, related to the appearance of polymethylene chains in these compounds.

Analysis of the PMR spectra of compounds III-XI studied shows that the addition of alcohol to the double bond of the vinyl group proceeds with the formation of α-addition products. In this case the proton signals of the ethylidene group $CHCH_3$ formed are represented in the spectra by a quartet (δ 5.44-5.64 ppm) and a doublet in the strong-field region (δ 1.51-1.57 ppm).

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TABLE 1. Properties of 1-(α-Alkoxyethyl)indoles III-XI

Compound	R	Yield, %	bp, °C (mm Hg)	n_D^{20}	d_4^{20}	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
III	n-C_4H_9	77	124 (2)	1,5372	1,0043	77,2	8,8	6,7	$C_{14}H_{19}ON$	77,4	8,8	6,5
IV	iso-C_4H_9	77	105 (2)	1,5350	0,9988	77,5	8,8	6,5	$C_{14}H_{19}ON$	77,4	8,8	6,5
V	sec-C_4H_9	61	97 (2)	1,5370	1,0043	76,9	8,8	6,8	$C_{14}H_{19}ON$	77,4	8,8	6,5
VI	C_5H_{11}	44	142—146 (2)	1,5310	0,9902	77,9	9,1	5,8	$C_{15}H_{21}ON$	77,9	9,1	6,0
VII	C_6H_{13}	73	158—160 (1)	1,5232	0,9736	78,0	9,3	5,9	$C_{16}H_{23}ON$	78,4	9,4	5,7
VIII	C_7H_{15}	55	170—173 (3)	1,5165	0,9688	78,8	9,7	5,8	$C_{17}H_{25}ON$	78,7	9,7	5,4
IX	C_6H_{11}	59	154 (2)	1,5495	1,0373	79,1	8,8	5,9	$C_{16}H_{21}ON$	79,0	8,7	5,7
X	C_3H_5	81	108—110 (2)	1,5622	1,0465	77,2	7,6	7,3	$C_{12}H_{15}ON$	77,6	7,5	7,0
XI	$C_6H_5CH_2$	63	164—166 (2)	1,5920	1,1071	81,1	6,8	5,8	$C_{17}H_{17}ON$	81,2	6,8	5,6

TABLE 2. Acute Toxicity Parameters and Antimicrobial Properties of 1-(α-Alkoxyethyl)indoles

Compound	LD_{50}, mg/kg	Minimal bacteriostatic concentration, μg/ml		
		Staph. aureus	E. coli	Ps. aeruginosa
II	1440	5 mg	5 mg	>200
IV	2000	>200	>200	>200
V	1340	>200	100	>200
VII	2900	>200	>200	>200
VIII	>2900	>200	>200	>200
IX	2900	>200	>200	>200
X	900	>200	>200	>200

EXPERIMENTAL PHARMACEUTICAL SECTION

The acute toxicity of the compounds was studied on nonpedigree white mice of both sexes, weighing 20-24 g each, with intraperitoneal administration. The LD_{50} values calculated by the Kerber method are listed in Table 2. In accordance with the K. K. Sidorov classification [3], the alkoxyethylindoles II, IV, V, VII-X studied can be classified as slightly toxic and practically nontoxic compounds.

The bacteriological activity of the compounds was determined by the method of serial dilutions in a liquid culture medium [4]. The microbial charge consisted of 250 thousand microbial cells in 1 ml. As the test cultures, we used *Staph. aureus* strain 209 P, *E. coli* strain 675, and *Ps. aeruginosa* strain 2789.

The experimental results (see Table 2) showed that sec-butoxyethylindole (V) inhibits the growth of *Escherichia coli* in a concentration of 100 μg/ml; 1-(α-methoxyethyl)indole (II) in a concentration of 5 mg/ml has a bacterial action on *Escherichia coli*, and bacteriostatic action on *Staphylococcus aureus*. The remaining compounds in a concentration of 200 μg/ml do not display inhibiting action toward all the test cultures used. Study of the antimicrobial activity in the compounds obtained showed that they have a moderate or weak antibacterial effect. Continuation of the search for biologically active compounds in this series is desirable.

EXPERIMENTAL CHEMICAL SECTION

The IR spectra were run on the UR-20 apparatus (GDR) in a microlayer. The PMR spectra were obtained on the RS-487 B spectrometer in CCl_4, using hexamethyldisiloxane as the internal standard. The purity and the individual state of the initial 1-vinylindole and the desired products were controlled by TLC on aluminum oxide, using ether–hexane (4:3) as a solvent. The spots on the chromatogram were detected in iodine vapors.

The initial vinylindole was synthesized by the method described in [5].

1-(α-Isobutoxyethyl)indole (IV). A 0.08 g portion of copper acetate, 0.04 g boric acid, and 0.24 ml of glacial acetic acid are added to a mixture of 5,8 g (0.05 mole) of I and 7.4 g (0.1 mole) of isobutyl alcohol. The mixture is heated to 120°C and stirred for 4 h. Compound IV is isolated from the reaction mixture by vacuum distillation in the form of a colorless oily liquid. Yield, 6.8 g.

1-(α-Alkoxyethyl)indoles II, III, V-IX, and XI are obtained by a similar procedure; their characteristics are given in Table 1.

1-(α-Allyloxyethyl(indole) (X). A 0.04 g portion of copper acetate, 0.02 g of boric acid, and 0.12 ml of glacial acetic acid are added to a mixture of 2.9 g (0.025 mmole) of I and 2.4 g of allyl alcohol. The mixture is heated at 100°C for 2 h 30 min. Compound X is isolated by vacuum distillation. Yield, 3.4 g.

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SYNTHESIS OF INDOLE DERIVATIVES AND THEIR ANTIVIRAL ACTIVITY

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Derivatives of indole and pyrrole are characterized by a broad spectrum of physiological activity; they have antimicrobial and fungicidal activity [1], display psychotropic [2] and antiinflammatory activity [3], and have narcotic, antihistaminic, and antiadrenalytic properties [4].

In the present article, we described the conditions of synthesis and the results of studying the antiviral activity of several indole derivatives (I-XVII) toward influenza virus (HK-17/68), classical fowl pestilence virus (FPV), para-influenza virus type 3, Venezuelan equine encephalomyelitis virus (VEL-230), adenovirus type 3, ECHO type 6, herpes simplex (strain L2), vaccines (dermovaccines produced at the Belorussian Scientific-Research Institute of Epidemiology and Microbiology), and coliphages T2 and f2. The viruses were obtained from the virus collection of the D. I. Ivanovskii Institute of Virology, Academy of Medical Sciences of the USSR.

4,5,6,7-Tetrahydroindole (I) and 1-vinyl-4,5,6,7-tetrahydroindole (II) were obtained by heterocyclization of cyclohexanone oxime with acetylene [5, 6]. (See Scheme on following page).

The reaction proceeds at 90-100°C in the presence of an alkali metal hydroxide—DMSO catalytic system at elevated or atmospheric pressure.

1-(2'-Butylthioethyl)-4,5,6,7-tetrahydroindole (III) was obtained by reacting butanethiol with II at 70-80°C in the presence of azoisobutyric acid dinitrile [7].

Perhydroindoles (IV) and (V) were synthesized by hydrogenation of I and 1-(2'-triethylsilylethyl)-4,5,6,7-tetrahydroindole over Raney nickel in ethanol at 150-160°C [8].

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