SYNTHESIS AND INVESTIGATION OF ANTIVIRAL PROPERTIES IN A SERIES OF DERIVATIVES OF 2-METHYL-5-HYDROXYINDOLE

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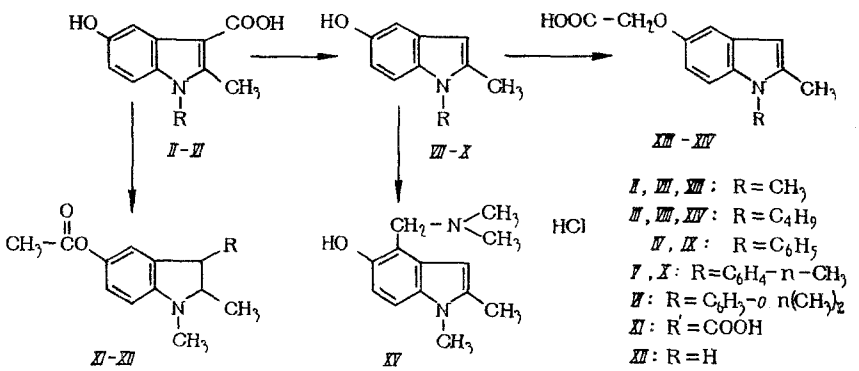
Continuing our investigations of various conversions of 1-alkyl(aryl)-2-methyl-3-carbethoxy-5-hydroxyindoles which we produced earlier [1-3], we found that the latter are unchanged during acid hydrolysis under normal conditions, while under the action of mineral acids they undergo decomposition under conditions of acid hydrolysis. The hydrolysis of 1-alkyl(aryl)-2-methyl-3-carbethoxy-5-hydroxyindoles* was successfully conducted only by fusing them with potassium hydroxide, to which a little water was added to lower the melting point of the alloy. 1-Alkyl(aryl)-2-methyl-5-hydroxyindole-3-carboxylic acids (II-VI), isolated from the salts by acidification with acetic acid, are rather stable under normal conditions. When heated above the melting point in an atmosphere of an inert gas, the acids (II-V) are decarboxylated, being converted in high yields to previously inaccessible 1-alkyl(aryl)-2-methyl-5-hydroxyindoles (VII-X). The properties of the derivatives of 5-hydroxyindoles that we obtained, as was shown by conversions of some of them (II, VII, and VIII), resemble the usual phenols. Acetylation of II and VII with acetic anhydride yielded O-acyl derivatives (XI-XII); interaction of the sodium derivatives of hydroxyindoles (VII, VIII) with chloroacetic acid resulted in the formation of substituted indolyl-5-hydroxyacetic acid (XIII-XIV); aminomethylation of 1,2-dimethyl-5-hydroxyindole (VII) under the action of bis-dimethylaminomethane led to 1,2-dimethyl-4-dimethylaminomethyl-5-hydroxyindole (XV):



The literature contains no information on investigations of the antiviral activity of derivatives of 5-hydroxyindole. We studied the antiviral activity (influenza virus) of compounds II-XV.

* 1-(m-xylyl)-2-methyl-3-carbethoxy-5-hydroxyindole (I) was produced in the present work.

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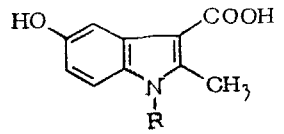
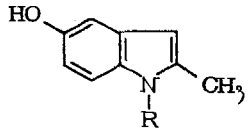
TABLE 1. 1-Alkyl(aryl)-2-methyl-5-hydroxyindole-3-carboxylic Acids



Compound	R	Yield, %	mp (in degrees), solvent for recrystallization	Found, %			Gross formula	Calc., %		
				C	H	N		C	H	N
III	n-C_4H_9	66	175-6 (dec.), acetone	68,09, 68,16	6,70, 6,58	5,78, 5,83	$C_{14}H_{17}NO_3$	67,99	6,94	5,66
IV	C_6H_5	87,5	Above 220° (dec.), methanol	71,65, 71,80	4,66, 4,80	5,24, 5,36	$C_{16}H_{13}NO_3$	71,90	4,90	5,24
V	C_6H_4-p-CH_3	87	Above 240° (dec.), methanol	72,23, 72,41	5,33, 5,34	4,62, 4,93	$C_{17}H_{15}NO_3$	72,58	5,37	4,98
VI	C_6H_3-o, p-$(CH_3)_2$	82	Above 240° (dec.), methanol	—	—	4,64, 4,60	$C_{18}H_{17}NO_3$	—	—	4,74

TABLE 2. 1-Alkyl(aryl)-2-methyl-5-hydroxyindoles



Compound	R	Yield, %	mp (in degrees), solvent for recrystallization	Found, %			Gross formula	Calc., %		
				C	H	N		C	H	N
VIII	n-C_4H_9	91	81-2°, benzene – petroleum ether (1 : 1)	76,82, 77,09	8,19, 8 40	6,70, 7,00	$C_{13}H_{17}NO$	76,88	8,43	6,89
IX	C_6H_5	89	118-8, benzene	80,35, 80,43	5,62, 5,86	5,89, 6,15	$C_{15}H_{13}NO$	80,69	5,86	6,27
X	C_6H_4-p-CH_3	94	103-4, benzene	81,31, 81,42	6,60, 6,40	5,87, 5,56	$C_{16}H_{15}NO$	80,98	6,37	5,90

Various concentrations of the solutions or suspensions of the substances studied with various amounts of lethal doses (LD_{100}) of influenza virus (strain APR-8) were mixed in test tubes in the experiments in vitro. The mixtures were exposed for 1 h at 12 and 14°, then used for intranasal infection of mice. Survival of the mice is evidence of antiviral activity of the substances. In experiments on chick embryos, the compounds were introduced into the alantoic sac of the embryos an hour before infection in the maximum tolerable concentrations and in lower concentrations. By comparing the titers of hemagglutinins and the infectious titers of the influenza virus, grown in the embryos into which the compounds had been introduced and in the controls, we judged the virus neutralizing activity of the substances. In experiments in vivo, the substance studied was injected into mice in the maximum tolerable dose and a dose half as large 1 h before infection with influenza virus; the animals received it in the same doses once a day during the following four days as well. By comparing the survival of the mice in the experimental and control groups, we evaluated the chemotherapeutic activity of the compounds. We described this procedure in detail in [4].

It was established that only 1-phenyl-2-methyl-5-hydroxyindole (IX) possesses virulicidic activity, pronounced although not high, neutralizing type A influenza virus, strain PR-8, in a concentration of 1 mg/ml. The remaining substances studied did not possess this activity in the indicated concentrations. In doses of 1 and 0.5 mg per embryo, IX had no inhibiting effect on the growth of APR-8 influenza virus in chick embryos. In mice with influenzal pneumonia, induced by A2 influenza virus (Frunze strain), IX, administered to the mice per os five times at doses of 1 and 0.5 g/kg, did not give any therapeutic effect.

EXPERIMENTAL

1-(m-Xylyl)-2-methyl-3-carbethoxy-5-hydroxyindole (I) was produced according to the method of synthesis of other N-arylindole derivatives described earlier [3]. For the experiment we used 54 g (0.5 mole) p-benzoquinone, 71.6 g (0.6 mole) acetoacetic ester, 121 g (0.5 mole) m-xylidine, 1400 ml dichloroethane, and 2-3 drops of concentrated hydrochloric acid. Yield 140 g (23.3%), mp 232-233° (from a dioxane-methanol mixture, 1.1). Found, %: C 73.87; 73.93; H 6.23; 5.95; N 4.21; 4.28. $C_{20}H_{21}O_3N$. Calculated, %: C 74.31; II 6.54; N 4.33.

1,2-Dimethyl-5-hydroxyindole-3-carboxylic Acid (II). To a melt obtained from 56 g (1 mole) potassium hydroxide and 10 ml of water, heated to 155°, we immediately added 23 g (0.1 mole) 1,2-dimethyl-3-carbethoxy-5-hydroxyindole. The melt was mixed for 5-10 min at 135-155° (until the evolution of gas bubbles ceased), cooled, and dissolved in three to four volumes of water. The solution obtained was acidified with acetic acid to an acid pH. The precipitate was filtered off, washed with water, dried in air, and recrystallized from methanol. Yield 15.7 g (76%), mp 180-181° (dec.). Found, %: C 64.32; 64.60; H 5.38; 5.41; N 6.78; 7.06. $C_{11}H_{11}NO_3$. Calculated, %: C 64.38; H 5.40; N 6.82. III-VI were produced analogously (Table 1).

1,2-Dimethyl-5-hydroxyindole (VII). We heated 13.7 g (0.07 mole) of the acid (II) for 3-5 min on a bath with Wood's metal at 200-215° in an atmosphere of inert gas. Yield 9.8 g (87%), mp 147-148° (from benzene). Found, %: C 74.60; 74.35; H 6.89; 6.87; N 8.67; 8.39. $C_{10}H_{11}NO$. Calculated, %: C 74.51; H 6.87; N 8.69. VIII, IX, and X were produced analogously (Table 2).

1,2-Dimethyl-5-acetoxyindole-3-carboxylic Acid (XI). We heated 10 g (0.05 mole) of the acid (II), 100 g (1 mole) acetic anhydride in 200 ml of acetone for 2 h on a water bath. Then the reaction solution was diluted with three volumes of water, the precipitate filtered and recrystallized from methanol. Yield 6 g (48%), mp 156-158° (dec.). Found, %: C 63.48; 63.39; H 5.55; 5.56; N 5.78; 6.00. $C_{13}H_{13}NO_4$. Calculated, %: C 63.15; H 5.30; N 5.67.

1,2-Dimethyl-5-acetoxyindole (XII). We heated 0.8 g (0.005 mole) of the indole (VII) and 0.6 g (0.006 mole) acetic anhydride for 2 h on a water bath at 100°, and then the reaction solution was diluted with water. Yield 0.5 g (50%), mp 107-108° (from methanol). Found, %: C 70.57; 70.68; H 6.32; 6.45; N 6.86; 6.96. $C_{12}H_{13}NO_2$. Calculated, %: C 70.91; H 6.44; N 6.89.

1,2-Dimethylindole-5-hydroxyacetic Acid (XIII). To a solution of sodium alcoholate, produced from 1.44 g (0.06 g-atom) of sodium and 90 ml absolute alcohol, we added 1.6 g (0.01 mole) VII and 2.85 g (0.03 mole) chloroacetic acid. The reaction solution was boiled for 3 h. The precipitate of the sodium salt was filtered, dissolved in water, and the aqueous solution acidified with acetic acid to an acid pH. The precipitate of the acid (XIII) was filtered and recrystallized from methanol. Yield 1.2 g (54%), mp 215-216° (dec.). Found, %: C 65.86; 66.10; H 6.06; 5.83; N 3.38; 3.56. $C_{12}H_{13}NO_3$. Calculated, %: C 65.79; H 5.97; N 6.39.

1-Butyl-2-methylindole-5-hydroxyacetic Acid (XIV) was produced under the conditions of the synthesis of XIII. Yield 3 g (58%), mp 155-156° (from methanol). Found, %: C 68.71; 69.00; H 7.27; 7.30; N 5.38; 5.25. $C_{15}H_{19}NO_3$. Calculated, %: C 68.98; H 7.32; N 5.31.

1,2-Dimethyl-4-dimethylaminomethyl-5-hydroxyindole Hydrochloride (XV). A mixture of 1.6 g (0.01 mole) VII and 1 g (0.01 mole) bis-dimethylaminomethane in solution in 5 ml absolute dioxane was heated for 2.5 h on a water bath. The solvent was distilled off under vacuum, the residue dissolved in absolute ether, and the ether solution treated with an insufficient amount of an ether solution of hydrogen chloride. Yield 1.2 g (47%), mp 163-164° (dec., from a methanol – acetone mixture, 1:1). Found, %: C 61.28; 60.99; H 7.53; 7.69; N 10.89; 11.20. $C_{13}H_{19}ClN_2O$. Calculated, %: C 61.21; H 7.52; N 10.99 (see Tables 1-2).

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