SYNTHESIS AND ANTIVIRAL ACTIVITY OF 2-PHENOXYMETHYL DERIVATIVES OF 5-HYDROXYINDOLE

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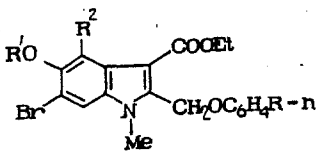
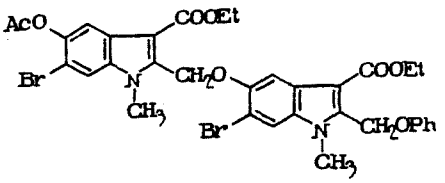
In a continuation of studies [1, 2] searching for new antiviral drugs and investigating the relationship between structure and activity, we carried out the synthesis of 2-phenoxymethyl derivatives of 5-acetoxy(hydroxy) indole.



II-V, VII-XVIII



VI

R=H(VI, IX, XI—XIII), OMe(V, X, XIV, XV), Br(II, VII, XVI, XVII), NO_2(III, VIII, XVIII), R^1=Ac(II—V); H(VII—XVIII); R^2=H(II—V, VII—X), CH_2NMe_2(XI, XV, XVI, XVIII); CH_2-piperidino(XII), CH_2-morpholino(XIII, XIV, XVII).

As starting compound, we used the previously described 1-methyl-2-bromomethyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole (I). When this was reacted in acetone with phenols and phenolamines containing methyl, bromo, or nitro groups at position 4, 2-phenoxymethyl derivatives of 5-acetoxyindole (II-V) were obtained. When unsubstituted phenol was used, we isolated 1-methyl-2-phenoxy-3-ethoxycarbonyl-5-(1-methyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindolyl-2-methoxy)-6-bromoindole (VI) as a by-product. Carrying out the same reaction in aqueous dioxane in the presence of KOH leads to O-deacylation, shown by reacting 5-acetoxyindole (I) with 4-methoxyphenol, which resulted in the isolation of the 5-hydroxyindole derivative (X). Alkaline hydrolysis of 5-acetoxyindoles II-V gave the corresponding 5-hydroxyindoles VII-X.

The IR spectra of these compounds lacked absorption bands in the region 1760-1770 cm^{-1}, corresponding to vibrations of the $COCH_3$ group, which are seen in the spectra of II-V, and contained absorption bands in the region 3240-3280 cm^{-1}, corresponding to the hydroxyl group.

When 5-hydroxyindoles VII-X were aminomethylated with bisaminomethanes, the corresponding 6-aminomethyl derivatives of 5-hydroxyindole (XI-XVIII) were obtained. Their IR spectra did not show an OH group, which is indicative of the zwitterionic nature of these compounds, by virtue of their containing a phenolic hydroxyl group at position 5 and a basic dialkylaminomethyl group at position 4.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a Perkin-Elmer 599 instrument (USA) in Vaseline. Mass spectra were obtained on a Varian MAT-112 mass spectrometer (Germany). Monitoring of individual compounds and the progress of reactions was done by chromatography on Silufol UV-254 plates in the systems $CHCl_3$, $CHCl_3$—MeOH (98:2), and benzene—acetone (9:1), with visualization by UV light.

Characteristics of the synthesized compounds II-XVIII are given in Table 1.

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TABLE 1. Characteristics of Synthesized Compounds II-XVIII

Compound	Yield, %	T_m*, °C	IR spectra, ν_{max}, cm^{-1}	Empirical formula
II	64,5	151—2	1770, 1680 (C=0)	$C_{21}N_{19}Br_2NO_5$
III	79,2	212—4	1760, 1680 (C=0)	$C_{21}H_{19}BrN_2O_7$
IV	72,5	148—50	1760, 1680 (C=0)	$C_{21}H_{20}BrNO_5$
V	68,3	130—2	1765, 1700 (C=0)	$C_{22}H_{22}BrNO_6$
VI	4,1	208—10	1765, 1690 (C=0)	$C_{34}H_{32}BrN_2O_8$
VII	84,9	214—5 (dec.)	1680, (C=0), 3260 (OH)	$C_{19}H_{17}Br_2NO_4$
VIII	79,18	229—30	1660 (C=0), 3240 (OH)	$C_{19}H_{17}BrN_2O_5$
IX	48	209—11 (dec.)	1650 (C=0), 3280 (OH)	$C_{19}H_{18}BrNO_4$
X	90,3	203—4 (dec.)	—	$C_{20}H_{20}BrNO_5$
XI Hydrochloride	77,2	114—5	1680 (C=0)	$C_{22}H_{25}BrN_2O_4$
XI	100	176—7	—	$C_{22}H_{25}BrN_2O_4 \cdot HCl$
XII	58,2	145—6	1685 (C=0)	$C_{25}H_{27}BrN_2O_4$
XIII Hydrochloride	59,1	167—9	1700 (C=0)	$C_{24}H_{25}BrN_2O_5$
XIV	100	78—80 (dec.)	—	$C_{25}H_{21}BrN_2O_6 \cdot HCl$
XV Hydrochloride	63,5	139—40	1700 (C=0)	$C_{23}H_{27}BrN_2O_5$
XV	100	116—8	—	$C_{23}H_{27}BrN_2O_5 \cdot HCl$
XVI Hydrochloride	60,7	165—7	1680 (C=0)	$C_{22}H_{24}Br_2N_2O_4$
XVI	100	184—5	—	$C_{22}H_{24}Br_2N_2O_4 \cdot HCl \cdot H_2O$
XVII Hydrochloride	78,2	178—80	1690 (C=0)	$C_{24}H_{26}Br_2N_2O_5$
XVIII	100	190—2	—	$C_{22}H_{26}Br_2N_2O_5$

*Compounds II, VI, XIII, XVI, and XVII were recrystallized from ethanol; XII from methanol; III, IV, V, X, XIV, and XV hydrochloride from acetone; XV and XI from isopropanol; VII and VIII from an ethanol—dioxane mixture; and XVI and XVIII hydrochlorides from an acetone—methanol—ether mixture.

The results of elemental analyses and molecular weight determinations agreed with calculated values.

Derivatives of 1-Methyl-2-phenoxymethyl-3-ethoxycarbonyl-5-acetoxy-6-bromoindole (II-V). The reaction mixture, consisting of 30 mmoles of indole I, 30 mmoles of the corresponding phenol, and 30 mmoles of anhydrous KOH in 150 ml dry acetone, as boiled for 5 h. The residue was filtered and the acetone evaporated, and compounds II-V were isolated. In the case of phenol, compound IV was isolated following recrystallization of the residue, and evaporation of the mother liquor yielded VI.

Derivatives of 1-Methyl-2-phenoxymethyl-3-ethoxycarbonyl-5-hydroxy-6-bromoindole (VII-X). A. To a suspension of 18 mmoles of acetoxyindole (II-V) in 150 ml absolute ethanol was added 40 mmoles KOH in 50 ml absolute ethanol, and this was stirred for 4 h at room temperature. Then 25 ml of water was added to the solution, which was acidified to pH 4. The residue was filtered, washed with water, and dried, which gave hydroxyindoles VII-X.

B. A mixture, consisting of 15 mmoles of indole I, 16 mmoles 4-methoxyphenol, and 16.6 mmoles K_2CO_3 in 50% aqueous dioxane was boiled for 5 h. The solvent was evaporated, water was added to the residue, and after filtration of sediment and washing with water, compound X was isolated.

Derivatives of 1-Methyl-2-phenoxymethyl-3-ethoxycarbonyl-4-dialkylaminomethyl-5-hydroxy-6-bromoindole (XI-XVIII). The reaction mixture, consisting of 10 mmoles of the indole (VII-X) and 20 mmoles of corresponding bis(dialkylamino)methane in 25 ml dry dioxane, was boiled for 5 h. The solvent and excess amine were evaporated under vacuum, and compounds XI-XVIII were obtained. The hydrochlorides were made by the usual method.

EXPERIMENTAL (BIOLOGY)

Antiviral activity of compounds was determined using the RNA-containing influenza virus A_0/FPV (H7N7) in primary cultures of chick embryo fibroblasts (CEF). Cell monolayers were inoculated with a dose of virus equal to 10 TCD_{50}. Antiviral activities of the compounds was assessed after 48 h, from inhibition of cytopathic activity of the virus, or from the

decrease in its plaque-forming activity. For this, cells monolayers were grown to confluence, and were inoculated with a dose of virus producing 40-50 plaques in the top-agar. The effectiveness of the compounds was determined after 48 h. Degree of inhibition of plaque-forming activity was expressed as percent of control.

Compounds were tested in concentrations of 5.0 and 2.5 μg/ml, which corresponded to 1/2 and 1/4 of the maximal dose tolerated by the cells.

Of ten compounds studied (IV, IX, XI-XVIII), only two showed weak activity. Compound XI inhibited plaque-forming activity by 40%, and XII lowered the infectious titer of the virus by 0.75 TCD_{50}.

Chemotherapeutic activity of compounds was studied using the model of mouse influenza pneumonia, induced by the virus A_2/Bethesda/63 (H2N2). Experiments were conducted using noninbred white mice, infected intranasally with a dose of virus equivalent to 10 LD_{50}. Activity of a compound was assessed by comparing the survival of animals in the control and experimental groups. The tested compounds IX, XIII, and XI hydrochloride displayed no antiviral activity.

LITERATURE CITED

1. A. N. Grinev, E. K. Panishcheva, A. A. Cherkasova, et al., Khim.-farm. Zh., No. 1, 52-55 (1987).
2. A. N. Grinev, E. K. Panishcheva, I. S. Nikolaeva, et al., ibid., No. 5, 575-577.