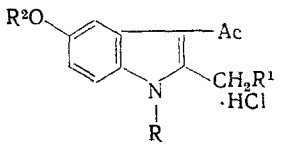
# AMINOALKYL-5- AND -6-HYDROXYINDOLES AND THEIR ANTIVIRAL ACTIVITY

E. K. Panisheva, É. S. Krichevskii,
I. S. Nikolaeva, A. N. Fomina,
A. A. Cherkasova, E. A. Golovanova,
and L. Yu. Krylova

UDC 615.281.8:547.751].012.1

Aminoalkyl-5-hydroxyindoles are of interest in possessing a wide spectrum of biological activity [1-3].



I—VI

R = Ph (I, IV), $C_6H_4OMe$-p (II, III, V, VI); $R^1$ = $NEt_2$ (I, II, IV, V), $N(CH_2CH_2)_2O$ (III, VI); $R^2$ = Ac (I—III), H (IV—VI).

We have now synthesized some novel aminoalkyl-5- and -6-hydroxyindoles (I-VI and XII) for testing for antiviral activity.

Compounds (I-III) were obtained by reacting 2-bromoethyl-5-hydroxyindoles [2] with secondary amines as described in [1], followed by hydrolysis to the phenols (IV-VI).

Since 4-dimethylamino-5-hydroxyindoles bearing a phenylthiomethyl substitutent at $C_2$ display antiviral activity [3], we also prepared the compound (XII).

Acetylation of 1-phenyl-2-methyl-3-ethoxycarbonyl-6-hydroxyindole [4] affords the 6-acetoxyindole (VII), which was then to be converted into 1-phenyl-2-bromoethyl-3-ethoxy-carbonyl-5-bromo-6-acetoxyindole (X). Since simultaneous bromination of (IV) in the benzene ring and at the $C_{(2)}$ methyl group was not possible, we obtained (X) by successive brominations of (VII).

Bromination of (VII) with N-bromosuccinimide (NBS) in $CCl_4$ with illumination in the presence of benzoyl peroxide afforded 1-phenyl-2-bromomethyl-3-ethoxy-carbonyl-6-acetoxyindole (VIII). In the PMR spectrum of this compound, the position and multiplicity of the signals for the aromatic protons were similar to those for the same protons in the starting material (VII), and in addition a singlet signal was present at $\delta$ = 4.93 ppm attributable to the protons of the methylene group in the 2-position of the indole ring. However, bromination of (VII) with bromine in acetic acid gave (IX), the PMR spectrum of which as compared with that of (VII) contained a singlet signal for the 2-methyl group at 2.53 ppm, signals for the protons in positions 4 and 7 with characteristic multiplicity, but no signal for a proton in the 5-position. Bromination of (VIII) with bromine in acetic acid gave the dibromide (X), which was also obtained by boiling (IX) with NBS in $CCl_4$ with illumination in the presence of benzoyl peroxide. Reaction of (X) with thiophenol in alcohol in the presence of KOH gave the 2-phenylthiomethyl derivative of 6-hydroxyindole (XI), which on reaction with bis(dimethy-lamino)methane was converted into (XII).

## EXPERIMENTAL (CHEMISTRY)

PMR spectra were obtained on a Varian XL-100 spectrometer (USA), internal standard TMS. The progress of the reactions and the purity of the products were followed by TLC on Silufol-254 plates in the system benzene—methanol (9:2), visualized in UV. The elemental analyses agreed with the calculated values.

S. Ordzhonikidze All-Union Research Institute for Pharmaceutical Chemistry, Moscow.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 2, pp. 189-191, February, 1989. Original article submitted November 18, 1987.

0091-150X/89/2302-0153$12.50  

1-Phenyl-2-dimethylaminomethyl-3-acetyl-5-acetoxyindole Hydrochloride (I). 1-Phenyl-2-bromomethyl-3-acetyl-5-acetoxyindole (0.5 g, 0.001 mole) was dissolved in 10 ml of dry benzene, 0.7 g (0.01 mole) of diethylamine added, and the mixture kept at ambient temperature. Completion of the reaction was determined by chromatography. The diethylamine hydrobromide which separated was filtered off and washed with dry benzene. The filtrate was evaporated to dryness, and the oily residue crystallized on adding light petroleum. The base (Ia) was filtered off and washed with light petroleum to give 0.43 g (64%) of product, mp 92-3°C (alcohol).

The hydrochloride (I) was obtained by acidifying an acetone solution of the base (Ia) with ethereal HCl. Yield 0.41 g (91%), mp 225-226°C (acetone–methanol).

1-(p-Methoxyphenyl)-2-diethylaminomethyl-3-acetyl-5-acetoxyindole Hydrochloride (II). Obtained as for (I). Yield 72.8%, mp 185-186°C (acetone).

1-(p-Methoxyphenyl)-2-morpholinomethyl-3-acetyl-5-acetoxyindole Hydrochloride (III) was obtained as for (I). Yield of the base (IIIa) 71%, mp 191-192°C (propan-2-ol).

Hydrochloride (III). Yield 94%, mp 190-191°C (acetone–methanol).

1-Phenyl-2-diethylaminomethyl-3-acetyl-5-hydroxyindole Hydrochloride (IV). The base (Ia) (3 g, 0.008 mole) was added to a solution of 0.45 g (0.008 mole) of KOH in 15 ml of methanol, and the mixture boiled under refux for 2 h. The solution was then poured into water, cooled, and the base (IVa) which separated was filtered off, and washed with water and alcohol to give 2.5 g (92.6%) of (IVa), mp 170-171°C (alcohol).

The hydrochloride (IV) was obtained as for (I), yield 93%, mp 224-5°C (decomp., acetone–methanol).

1-(p-Methoxyphenyl)-2-diethylaminomethyl-3-acetyl-5-hydroxyindole Hydrochloride (V) was obtained as for (IV). The yield of the base (Va) was 88.9%, mp 219-220°C (alcohol).

Hydrochloride (V). Yield 90%, mp 206-7°C (acetone–methanol).

1-(p-Methoxyphenyl)-2-morpholinomethyl-3-acetyl-5-hydroxyindole Hydrochloride (VI) was obtained as for (IV). The yield of the base (VIa) was 81.3%, mp 191-192°C (alcohol).

Hydrochloride (VI). Yield 90%, mp 210-211°C (acetone–methanol).

1-Phenyl-2-methyl-3-ethoxycarbonyl-6-acetoxyindole (VII). A suspension of 2.8 g (0.01 mole) of 1-phenyl-2-methyl-3-ethoxycarbonyl-6-hydroxyindole [4], 10 ml of acetic anhydride, and 10 ml of pyridine was boiled for 5 h and kept overnight at 20°C. The mixture was then poured into water, and kept for three hours. The solid was filtered off, and washed with 8% HCl, water, and alcohol, until neutral, to give 2.5 g (74.2%) of (VII), mp 140-142°C (alcohol).

1-Phenyl-2-bromomethyl-3-ethoxycarbonyl-6-acetoxyindole (VIII). A suspension of 3.4 g (0.01) of (VII), 2 g of N-bromosuccinimide, and 40 ml of $CCl_4$ was boiled in the presence of a catalytic amount of benzoyl peroxide for 4.5 h while illuminating with a 300 W lamp. The hot reaction mixture was filtered to remove succinimide, and the filtrate evaporated under reduced pressure. The residue was treated with a hot mixture of $CCl_4$ and light petroleum (20 ml, 1:1), cooled, and the solid filtered off and washed with light petroleum and alcohol to give 2.8 g (70%) of (VIII), mp 114-116°C (alcohol).

1-Phenyl-2-methyl-3-ethoxycarbonyl-5-bromo-6-acetoxyindole (IX). To a suspension of 3.4 g (0.01 mole) of (VII) in 30 ml of glacial acetic acid was added with stirring at 18-20°C 1 ml (0.02 mole) of bromine in 10 ml of glacial acetic acid. The mixture was stirred for 2 h, and the solid filtered off, and washed with 5 ml of glacial acetic acid, water, and alcohol to give 2.8 g (66.8%) of (IX), mp 156-158°C (alcohol).

1-Phenyl-2-bromomethyl-3-ethoxycarbonyl-5-bromo-6-acetoxyindole (X). Method A. A mixture of 6.2 g (0.015 mole) of (IX) and 4 g (0.024 mole) of N-bromosuccinimide was boiled in $CCl_4$ in the presence of a catalytic amount of benzoyl peroxide, with stirring. The product (X) was isolated as for (VIII), yield 5 g (68%), mp 173-176°C (decomp. alcohol).

Method B. Bromination of (VIII) with bromine in glacial acetic acid as for (IX) gave (X) in 64.5% yield, mp 174-176°C (decomp., alcohol). A mixed melting point with samples of the materials obtained by methods A and B gave no depression.

1-Phenyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-bromo-6-hydroxyindole (XI). To a

solution of 0.84 g (0.015 mole) of KOH in 10 ml of absolute alcohol was added with stirring at 20°C a solution of 0.55 ml (0.005 mole) of thiophenol in 3 ml of absolute alcohol. The mixture was stirred for ten minutes, then a solution of 2.5 g (0.005 mole) of (X) in 40 ml of absolute alcohol was added, the mixture stirred for 5 h, and evaporated to 1/3 of its volume. To the residue was added a solution of 1.5 ml of acetic acid in 75 ml of water, the mixture heated at 50°C with vigorous stirring for 10-15 min, cooled, filtered, and the solid washed with water to give 2.04 g (85%) of (XI), mp 205-206°C (alcohol).

1-Phenyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-bromo-6-hydroxy-7-dimethylaminomethylindole (XII). To a solution of 4 g (0.009 mole) of (XI) in 25 ml of dry dioxane was added 2.4 ml (0.015 mole) of bis(dimethylamino)methane, and the mixture boiled for 2.5 h. It was then evaporated, and the residue dissolved in absolute alcohol and treated with a solution of HCl in absolute alcohol to give 4.1 g (87.2%) of (XII), mp 176-178°C (alcohol).

## EXPERIMENTAL (BIOLOGY)

The biological testing of (I)-(XII) was carried out as described in [2].

The activity of the 5- and 6-hydroxyindoles was examined against influenza virus. It was found that the 5-hydroxyindoles (IV) and (V) in concentrations of 5.0 and 2.5 μg/ml (1/4 and 1/8 of the MTC) affected the reproduction of the influenza virus in chicken embryo fibroblast culture, reducing the infective titer of the virus by 1.0 lg $CDT_{50}$.

In model influenzal pneumonia in mice, the most active of the compounds tested was the hydrochloride (IV). In doses of 60 and 30 mg/kg, this compound when administered per os reduced the mortality of the animals by 40%. Compounds (V) and (VI) were less active, reducing the mortality in mice with influenzal pneumonia in a dose of 60 mg/kg per os by no more than 30%. When the dose was decreased to 30 mg/kg, they were inactive.

It is interesting that none of the 5-hydroxyindoles had viral inhibitory activity on the influenza virus.

Among the 6-hydroxyindoles (VIII) was weakly active. On culturing the virus in the presence of (VIII) at a dose of 5 μg/ml, the viral titer was reduced by 0.75 lg $CDT_{50}$, and at a dose of 2.5 μg/ml, by 1.0 lg $CDT_{50}$.

## LITERATURE CITED


1. A. N. Grinev, E. K. Panisheva, I. S. Nikolaeva, et al., Khim.-farm. Zh., No. 5, 575 (1987).
2. E. K. Panisheva, N. I. Mikerova, I. S. Nikolaeva, et al., ibid., No. 12, 1455 (1988).
3. E. K. Panisheva, A. N. Fomina, I. S. Nikolaeva, et al., ibid., No. 5, 565 (1988).
4. V. I. Shvedov, E. K. Panisheva, T. F. Vlasova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 10, 1354 (1973).