SYNTHESIS AND ANTIVIRAL ACTIVITY OF 5-OXYINDOLE DERIVATIVES

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

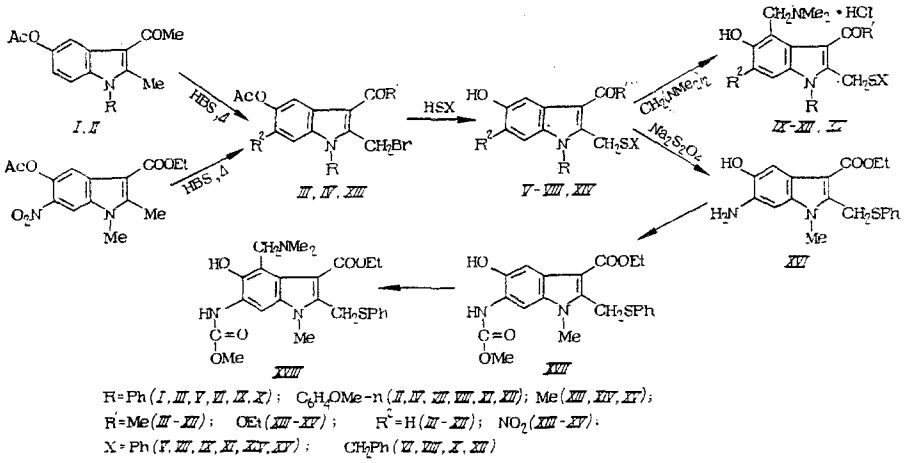
UDC 615.281.8:547.751].012.1

The 4-dimethylaminomethyl derivatives of 5-oxyindole that have a phenylthiomethyl substituent in position 2 of indole ring are known to possess antiviral activity [3].

As a continuation of those studies we used the 3-acetyl-5-oxyindoles [1] as starting compounds to synthesize 2-phenyl(benzyl)thiomethyl derivatives of 3-acetyl-5-oxyindole (V-VIII) and 2-phenylthiomethyl-3-ethoxycarbonyl-5-oxy-6-nitro(amino)indoles (XIV, XVI).

We had assumed that the 3-acetyl-5-acetoxyindoles (I, II) would be brominated by N-bromosuccinimide (NBS) in CCl_4 at position 6 of the benzene ring in the same way that derivatives of 3-ethoxycarbonyl-5-acetoxy(methoxy)indole are brominated [4]. However, judging by the PMR spectra, substitution took place in the CH_3 group at $C_{(2)}$ which confirms the presence of CH_2Br group proton signals (δ 4.99 ppm) at $C_{(2)}$. The PMR spectrum also has proton signals at positions 4, 6, and 7 with their characteristic multiplet property.

When 2-bromomethyl derivatives of 3-acetyl-5-acetoxyindole (III, IV) were reacted with thiophenol and benzylmercaptan we obtained the corresponding 2-phenyl(benzyl)thiomethyl-5-oxyindoles (V-VIII). The latter were aminomethylated with bis(dimethylamino)methane with the formation of 4-dimethylaminomethyl-5-oxyindoles (IX-XII).



R = Ph (I, III, V, VII, IX, XI); C_6H_4OMe-n (II, IV, VI, VIII, X, XII); Me (XIII, XIV, XV);
R' = Me (III-XII); OEt (XIII-XV); R^2 = H (III-XII); NO_2 (XIII-XV);
X = Ph (V, VII, IX, XI, XIV, XV); CH_2Ph (VI, VIII, X, XII)

The corresponding derivatives XIII-XV were synthesized in a similar manner from 1,2-dimethyl-3-ethoxycarbonyl-5-oxy-6-nitroindole. By reducing compound XIV with sodium hydrosulfite in an alkaline medium we synthesized 1-methyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-oxy-6-aminoindole (XVI) which when reacted with chlorocarbonate was converted to the methoxycarbonyl amino derivative of 5-oxyindole (XVII). Aminomethylation of the latter resulted in compound (XVIII). The element analysis values corresponded to the calculated ones.

S. Ordzhonikidze All-Union Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 12, pp. 1455-1458, December, 1988. Original article submitted October 20, 1987.

EXPERIMENTAL CHEMISTRY

The PMR-spectra were recorded on a XL-100 Varian (USA) spectrometer. TMS was the internal standard. IR-spectra were recorded on a Perkin-Elmer 599 (USA) spectrophotometer in the form of a suspension in petroleum jelly. Reaction progress and compounds purity were controlled by TLC on Silufol UV-254 plates in a 9:2 benzene–methanol system. Development in UV light.

1-Phenyl-2-methyl-3-acetyl-5-acetoxyindole (I). A 15 g (0.06 mole) portion of 1-phenyl-2-methyl-3-acetyl-5-oxyindole [5] was mixed with 75 ml of Ac_2O and boiled with a reflux condenser for 3.5 h. The reaction solution was cooled to 50-60°C and decanted into water. The resultant precipitate was filtered off and washed with water and alcohol. Yield was 17 g (97.7%), mp 153-154°C (ethanol). $C_{19}H_{17}NO_3$.

1-(n-Methoxyphenyl)-2-methyl-3-acetyl-5-acetoxyindole (II) was obtained in the same manner as compound I (see [5] for starting indole). Yield 98%, mp 185-186°C (acetone). $C_{20}H_{19}NO_4$.

1-Phenyl-2-bromomethyl-3-acetyl-5-acetoxyindole (III). A 0.8 g (0.045 mole) portion of NBS was added to a suspension of 1 g (0.003 mole) of I in 20 ml of CCl_4 and the reaction mixture was boiled with stirring for 1 h (end of reaction was determined chromatographically). When the reaction was completed the succinimide was removed from the reaction mass by filtration. When the filtrate was cooled the resultant precipitate was filtered off and washed with CCl_4. Yield of III was 1.21 (96%), mp 161-162°C (hexane–ethyl acetate). $C_{19}H_{16}BrNO_3$.

1-(n-Methoxyphenyl)-2-bromomethyl-3-acetyl-5-acetoxyindole (IV) was obtained in the same manner as compound III. Yield 47%, mp 175-176°C (hexane–ethyl acetate). $C_{20}H_{18}BrNO_4$.

1-Phenyl-2-phenylthiomethyl-3-acetyl-5-oxyindole (V). A 1.68 g (0.03 mole) portion of KOH was dissolved in 40 ml of absolute alcohol at 60-70°C. After the solution was cooled to room temperature, a solution of 1.1 g (0.01 mole) of thiophenol in 2 ml of absolute alcohol and a suspension of 3.9 g (0.01 mole) of compound III in 40 ml of absolute alcohol was added. The reaction mixture was stirred for 1 h at room temperature after which it was boiled on a water bath for 2 h. The solvent was vaccum distilled to $^2/_3$ of its volume. A solution of 1.8 g (0.03 mole) of AcOH in 100 ml of water heated to 35-40°C was added upon vigorous stirring to the remaining reaction mass. The mass was then stirred for 30 min after which the precipitate was filtered off and washed with water. Yield 3.7 g (88.3%), mp 218-219°C (absolute alcohol). $C_{23}H_{19}NSO_2$.

1-Phenyl-2-benzylthiomethyl-3-acetyl-5-oxyindole (VI) was obtained in the same manner as compound V. Yield 98.7%, mp 205-206° with (i-PrOH), $C_{24}H_{21}NSO_2$.

1-(n-Methoxyphenyl)-2-phenylthiomethyl-3-acetyl-5-oxyindole (VII) was obtained in the same manner as compound V. Yield 96.1%, mp 205-206°C (acetone). $C_{24}H_{21}NSO_3$.

1-(n-Methoxyphenyl)-2-benzylthiomethyl-3-acetyl-5-oxyindole (VIII) was obtained in the same manner as compound V. Yield 99%, mp 239-240°C (acetone–dioxane). $C_{25}H_{23}NSO_3$.

1-Phenyl-2-phenylthiomethyl-3-acetyl-4-dimethylaminomethyl-5-oxyindole hydrochloride (IX). A 0.76 g (1.26 ml, 0.0075 mole) of bis(dimethylamino)methane was added to a solution of 1.85 g (0.005 mole) of V in 20 ml of absolute dioxane and the reaction solution was boiled for 2.5 h. The solvent was then distilled to dryness. Yield of the IXa base was 2 g (93.9%), mp 157-158°C (acetone). $C_{26}H_{26}N_2SO_2$.

Compound IX was obtained by acidifying the acetone solution of base IXa with an HCl ester solution. Yield of IX was 83%, mp 168-169°C (acetone–methanol). $C_{26}H_{27}ClN_2SO_2$.

1-Phenyl-2-benzylthiomethyl-3-acetyl-4-dimethylaminomethyl-5-oxyindole hydrochloride (X) was obtained in the same manner as compound IX. Yield of the base Xa was 91.3%, mp 141-142°C (acetone). $C_{27}H_{28}N_2SO_2$. Yield of X was 89%, mp 197-198°C (acetone–methanol). $C_{27}H_{29}ClN_2SO_2$.

1-(n-Methyoxyphenyl)-2-phenylthiomethyl-3-acetyl-4-dimethylaminomethyl-5-oxyindole (XI) was obtained in the same manner as compound IX. Yield of XI was 85%, mp 147-148°C (i-PrOH). $C_{27}H_{28}N_2SO_3$.

1-(n-Methoxyphenyl)-2-benzylthiomethyl-3-acetyl-4-dimethylaminomethyl-5-oxyindole hydrochloride (XII) was obtained in the same manner as compound IX. Yield of the base XIIa was 90.3%, mp 108-109 C (i-PrOH). $C_{28}H_{30}N_2SO_3$.

Yield of XII was 95%, mp 191-193°C (acetone–methanol). $C_{28}H_{31}ClN_2SO_3$.

1-Methyl-2-bromomethyl-3-ethoxycarbonyl-5-acetoxy-6-nitroindole (XIII). A mixture of 8.7 g (0.027 mole) of 1,2-dimethyl-3-ethoxycarbonyl-5-acetoxy-6-nitroindole [2], 7.9 g (0.044 mole) of NBS and a catalytic quantity of benzoyl peroxide in 200 ml of dry CCl_4 was boiled for 4 h while illuminated by a 200 watt bulb. The succinimide precipitate was filtered off and washed with CCl_4. The precipitate formed from the mother liquor upon cooling was filtered off, washed with cooled CCl_4, and dried. Yield 7.9 g (67%), mp 180-182°C (hexane–ethyl acetate. $C_{15}H_{15}BRN_2O_6$.

1-Methyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-oxy-6-nitroindole (XIV) was obtained in the same manner as compound V. Yield 79%, mp 126-128°C (acetone). $C_{19}H_{18}N_2SO_5$.

1-Methyl-2-phenylthiomethyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-oxy-6-nitroindole (XV). A 0.4 g (0.004 mole) portion of bis(dimethylamino) methane was added to a solution of 1 g (0.0026 mole) of compound XIV in 50 ml of glacial AcOH. The reaction mixture was boiled for 4 h, then cooled and decanted into water. The AcOH was neutralized with 68 ml of 22% aqueous ammonia solution. The resultant oil was extracted with $CHCl_3$. The extract was dried with $MgSO_4$. The $CHCl_3$ was distilled off and the residue was crystallized. The yield of the base XVa was 0.35 g (30%), mp 101-103°C (methanol), $C_{22}H_{25}N_3O_5S$.

The hydrochloride of XV was obtained in the same manner as IX. Yield was 87.5%, mp 167-168°C (acetone–methanol). $C_{22}H_{26}ClN_3O_5S$

1-Methyl-2-phenylthiomethyl-3-ethoxycarbonyl-5-oxy-6-aminoindole (XVI). A solution of 4.3 g (0.03 mole) of sodium hydrosulfite in 20 ml of water was added to a mixture of 5.2 g (0.013 mole) of XIV in 72 ml of dioxane and 2.4 g (0.06 mole) of NaOH in 40 ml of water at 80°C. The reaction mixture was heated on a boiling water bath for 1 h after which it was cooled and 3.6 ml of AcOH was added. The precipitate was filtered off and washed with water and ether. Yield was 3.6 g (78%), mp 222°C (decomp. dioxane). $C_{19}H_{20}N_2O_3S$.

1-Methyl-2-phenylthiomethyl-3-methyl-3-ethoxycarbonyl-5-oxy-6-methoxycarbonylaminoindole (XVII). A 0.402 g (0.0051 mole) portion of pyridine and 0.48 g (0.0051 mole) of ClCOOMe was added to a solution of 1.65 g (0.0046 mole) of XVI in 450 ml of dioxane at room temperature. The reaction mixture was stirred for 1 h and the dioxane was evaporated to $^3/_4$ of its volume. The resultant precipitate was filtered off, washed with water and dried. Yield was 1.3 g (68%), mp 237-239°C (ethanol). IR-spectrum, ν_{max}, cm^{-1}: 3600-3100 (OH, NH), 3440 (NH), 1740 (CO amid.), 1660 (CO complex ester). $C_{21}H_{22}H_2O_5S$.

1-Methyl-2-phenylthiomethyl-3-ethoxycarbonyl-4-dimethylaminomethyl-5-oxy-6-methoxycarbonylaminoindole (XVIII) was obtained in the same manner as compound IX. Yield was 43%, mp 153-155°C (methanol). $C_{21}H_{22}N_2O_5S$.

EXPERIMENTAL BIOLOGY

The antiviral activity of the synthesized compounds was tested against influenza type A viruses strain A/Bethesda/63 (H2N2), A/FPV (H7N7). Virus-inhibiting activity of the substances was tested in a primary trypsinized culture of chick embryo fibroblast cells which was inoculated with 1-100 50% tissue cytopathic doses (TCD_{50}) of the virus. The compounds were employed at concentrations which were $^1/_4$ and $^1/_8$ of the maximum tolerated concentrations for the cell culture. The results were computed on the basis of the reduction in the infectious titer and the patch-forming activity of the virus in comparison to the control.

The substances chemotherapeutic activity was tested on a mouse pneumonia model induced by intranasal inoculation of the influenza virus. The substances were administered to the mice per os at 60 and 30 mg/kg ($^1/_4$ and $^1/_8$ of the maximum tolerated dose) in accordance with a prophylactic-therapeutic schedule (24 h and 6 h before infection, and at intervals of 24, 48, and 72 h after infection).

Activity was judged by the reduction in influenza pneumonia mortality in the treated mice in comparison to the control. Pearson's χ^2 coefficient was used for the statistical processing.

Seven of the nine tested compounds (V, VIII-XI, XIV, and XVII) exhibited inhibition of influenza virus reproduction in a culture of chick embryo fibroblast cells and reduced patch formation by 35-50% in comparison to the control when employed at a concentration of from 2.5 to 10 μg/ml.

In an influenza pneumonia model in mice four compounds (V, IX–XI) exhibited antiviral activity when administered per os in accordance with a prophylactic-therapeutic scheduleat doses of 30 and 60 mg/kg where they reduced the animal mortality rate by 30-40% in comparison to the control ($P < 0.05$).

In analyzing the structure-action relationship of the tested 5-oxyindole derivatives, one can note that the compounds that have a phenyl substituent in position 1 of the indole ring (V, IX, X) exhibit activity against the influenza virus both in the cell culture and the model experiments on the animals.

Thus, we have established the antiviral activity against the influenza virus of synthesized derivatives of 5-oxyindole in in vitro experiments. The activity of the tested compounds did not exceed that of the recognized antiinfluenza preparation rimantadine.

LITERATURE CITED

1. A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, Zh. Obshch. Khim., 26, 1449 (1956).
2. E. Ya. Zinchenko, L. G. Yudin, and A. N. Kost, Khim. Geterotstikl. Soed., No. 12, 1646 (1973).
3. E. K. Panisheva, A. N. Fomina, I. S. Nikolaeva et al., Khim.-farm. Zh., No. 5, 565-569 (1988).
4. F. A. Trofimov, N. G. Tsyshkova, and A. N. Grinev, Khim. Geterotsikl. Soed., No. 3, 308 (1973).
5. V. I. Shedov, Condensation of Acetylacetone Imines with 1,4 Quinones [in Russian], Candidate of Chemical Sciences dissertation abstract, Moscow (1962).

MOLECULAR STRUCTURE-ACTION RELATIONSHIP IN NITRITE INHIBITORS OF HEMOGLOBIN OXIDATION

L. Kh. Kostenko, É. G. Rozantsev, and V. A. Savel'ev

UDC 615.31:547.418].015.4:616.155.16].07

The targeted selection of biologically active compounds such as inhibitors of nitrite oxidation of hemoglobin (Hb) and the study of their mode of action are quite essential to the prevention and clinical treatment of methemoglobinemia, particularly the nitrite variety which is caused by the broad use of nitroso compounds (organic nitro compounds, nitrites, nitrogen oxides) in a number of industrial sectors [2].

The purpose of the present work is to study the connection between the molecular structure and functional activity of new potential substances, benzoic acid derivatives, that inhibit the nitrite oxidation of oxyhemoglobin (HbO_2). The compounds under examination belong to a large class of organic compounds that are important as semiproducts in the synthesis of medicinal preparations. Some of them are used as preservatives [n-oxybenzoic acid (I)] and in pharmacology [salicylic (II) and o-acetoxybenzoic (VIII) acids] [4].

EXPERIMENTAL

HbO_2 isolated from cattle by method [11] with certain modifications was used in our experiments. The concentration of HbO_2 and MetHb was measured spectrophotometrically with acetone cyanohydride [2]. The kinetics of the nitrite oxidation of HbO_2 in the presence of inhibitors was recorded on a SF-26 spectrometer at 630 nm pH 5.9 and 7.17 by the previously described method [1]. Compounds of chemically pure grade were used in the experiments.

Institute of Chemical Physics, USSR Academy of Sciences, Moscow.

Translated from Khimiko-farmatsevtcheskii Zhurnal, Vol. 21, No. 12, pp. 1458-1461, December, 1988. Original article submitted June 26, 1987.

0091-150X/88/2212-0904$12.50