SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 1-ALKYL(ARYL)-5-METHOXY(4,5-DIMETHOXY)-6-BROMOINDOLES

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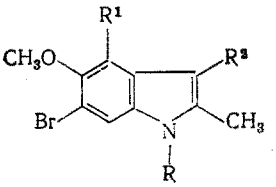
5-Hydroxy- and 4,5-dihydroxyindoles are of interest as biologically active compounds [2, 4-6]. It has previously been shown [1] that O-methyl derivatives of 5-hydroxyindole undergo hydrolysis to give indole-3-carboxylic acids. The latter in turn on decarboxylation are converted into 5-methoxyindoles with a free β-position.

We have now synthesized some novel 5-methoxyindole-3-carboxylic acids with bromine in the 6-position of the ring (Ia, b). Decarboxylation of these compounds in quinoline has afforded 5-methoxy-6-bromoindoles with a free β-position (IIa, b). These compounds, like 4,5-dimethoxy-6-bromoindole (IIc) [2], are of interest as starting materials for the synthesis of analogs of biologically active compounds.

The Vilsmaier reaction has given 1,2-dimethyl-3-formyl-5-methoxy- and 1-phenyl-2-methyl-3-formyl-4,5-dimethoxy-6-bromoindole (IIIa, c) and their thiosemicarbazones (IVa, c).

Aminomethylation of 1,2-dimethyl-5-methoxy-6-bromoindole (IIa) gives the 5- methoxygramine (Va). 1-Phenyl-2-methyl-3-dimethylaminomethyl-4,5-dimethoxy-6-bromoindole (Vc), previously obtained by us [1], on conversion to the methiodide and treatment with sodium cyanide gives 1-phenyl-2-methyl-3-cyanomethyl-4,5-dimethoxy-6-bromoindole (VI).

The antiviral activity of these compounds has been examined.



I — VI

R = Me (Ia; IIa; IIIa; IVa; Va); Ph (Ib; IIb,c; IIIc; IVc; Vc; VI)
R¹ = H (Ia, b; IIa, b; IIIa; IVa; Va); OCH_3 (IIc; IIIc, IVc; Vc; VI)
R² = COOH (Ia, b); H (IIa-c); CHO (IIIa, c); CH=N—NH—C(=S)NH_2 (IVa, c); $CH_2N(CH_3)_2$ (Va, c); CH_2CN (VI)

EXPERIMENTAL CHEMICAL PART

1,2-Dimethyl-5-methoxy-6-bromoindole-3-carboxylic Acid (Ia). To a melt of 50.5 g (0.9 mole) of potassium hydroxide in 9 ml of water, heated to 155-160°C, was added 29 g (0.09 mole) of 1,2-dimethyl-3-ethoxycarbonyl-5-methoxy-6-bromoindole [3]. The mixture was stirred vigorously at 155-160°C for 25-30 min. The temperature of the melt was the raised to 200°C, and stirring continued until the mass solidified. The resulting potassium salt was cooled and dissolved in water. The solution obtained was neutralized with acetic acid (54 g, 0.9 mole), and the precipitated acid (Ia) filtered off, washed with water, and dried to give 18.5 g (70%) of product, mp 220-222°C (from dimethylformamide) Found, %: C 48.13; H 4.00; Br 26.87; N 4.73. $C_{12}H_{12}BrNO_3$. Calculated: C 48.34; H 4.06; Br 26.80; N 4.70.

1-Phenyl-2-methyl-5-methoxy-6-bromoindole-3-carboxylic Acid (Ib). From 14 g (0.25 mole) of potassium hydroxide, 2.5 ml of water, and 12 g (0.025 mole) of 1-phenyl-2-methyl-3-

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ethoxycarbonyl-5-methoxy-6-bromoindole [3] there was obtained, using the same procedure as for (Ia), 8 g of (Ib) (86.5%), mp 219-220°C (from dimethylformamide). Found, %: C 56.39; H 4.00; Br 22.11; N 4.03. $C_{17}H_{14}BrNO_3$. Calculated, %: C 56.68; H 3.92; Br 22.18; N 3.89.

1,2-Dimethyl-5-methoxy-6-bromoindole (IIa). In a flask fitted with an air condenser was heated a mixture of 10 ml of quinoline and 1.7 g (0.005 mole) of the acid (Ia) at 220-225°C, until the evolution of carbon dioxide ceased. The solution was then poured into water, and acidified with hydrochloric acid. The solid was filtered off, washed thoroughly with water, and dried to give 1.3 g (92.8%) of (IIa), mp 95-96°C (from propan-2-ol). Found, %: C 51.91; H 4.90; Br 31.45; N 5.42. $C_{11}H_{12}BrNO$. Calculated, %: C 51.99; H 4.76; Br 31.45; N 5.51.

1-Phenyl-2-methyl-5-methoxy-6-bromoindole (IIb). From 1.7 g (0.005 mole) of (Ib) and 10 ml of quinoline there was obtained, using the procedure described for (IIa), 1.3 g (86.6%) of (IIb), mp 88-90°C (from propan-2-ol). Found, %: C 60.73; H 4.38; Br 25.20; N 4.45. $C_{16}H_{14}BrNO$. Calculated, %: C 60.77; H 4.46; Br 25.27; N 4.43.

1,2-Dimethyl-3-formyl-5-methoxy-6-bromoindole (IIIa). To 6.9 g (0.094 mole) of dimethylformamide (DMF) was added slowly with stirring at 10°C 3.4 g (0.022 mole) of freshly-distilled phosphoryl chloride, the mixture stirred for a further 30 min at 10°C, and a solution of 5.08 g (0.02 mole) of (IIa) in 10 ml of DMF added dropwise over 20 min. The mixture was stirred for 1 h at 20°C and 45 min at 35°C, poured into water, and treated with 2 M sodium hydroxide. It was then heated to the boil, cooled, and the solid filtered off and washed with water to give 4.8 g (85.7%) of (IIIa), mp 262-263°C (from DMF). Found, %: C 51.26; H 4.53; Br 28.29; N 4.91. $C_{12}H_{12}BrNO_2$. Calculated, %: C 51.08; H 4.29; Br 28.32; N 4.97.

1-Phenyl-2-methyl-3-formyl-4,5-dimethoxy-6-bromoindole (IIIc). A mixture of 1 g (0.003 mole) of 1-phenyl-2-methyl-4,5-dimethoxy-6-bromoindole (IIc) [2], 20 ml of DMF, and the Vilsmaier reagent, prepared from 0.66 g (0.009 mole) of DMF and 1.4 g (0.009 mole) of phosphoryl chloride was heated on the boiling water bath for 14 h. The reaction mixture was diluted with 50 ml of water, and the solid which separated was filtered off, washed with water, dried, and recrystallized from propan-2-ol to give 0.65 g (60%) of (IIIc), mp 143-145°C. Found, %: C 58.1; H 4.4; Br 21.3; N 3.5. $C_{18}H_{16}BrNO_3$. Calculated, %: C 57.8; H 4.3; Br 21.3; N 3.7.

1,2-Dimethyl-3-formyl-5-methoxy-6-bromoindole Thiosemicarbazone (IVa). A hot solution of 1 g (0.004 mole) of (IIIa) in 10 ml of DMF was mixed with a hot solution of 0.52 g (0.004 mole) of thiosemicarbazide hydrochloride and 0.4 g (0.004 mole) of sodium acetate in 80 ml of ethanol. The resulting solution was boiled for 1.5 h, cooled, the solid filtered off, and washed with alcohol to give 1 g (83.3%) of (IVa), mp 243-245°C. Found, %: C 43.55; H 4.1; Br 22.84; N 15.74; S 9.24. $C_{13}H_{15}BrN_4SO$. Calculated, %: C 43.95; H 4.25; Br 22.5; N 15.8; S 9.0.

1-Phenyl-2-methyl-3-formyl-4,5-dimethoxy-6-bromoindole Thiosemicarbazone (IVc). A mixture of 0.65 g (0.017 mole) of (IIIc), 0.22 g (0.017 mole) of thiosemicarbazide hydrochloride, 0.14 g (0.017 mole) of sodium acetate, and 50 ml of ethanol was boiled for 1 h. The solution was cooled to 20°C, and the solid which separated was filtered off, washed with alcohol, and dried to give 0.92 g (40%) of (IVc), mp. 234-235°C (from acetic acid). Found, %: C 51.2; H 4.3; Br 17.9; N 12.4; S 7.1. $C_{19}H_{19}BrN_4SO_2$. Calculated, %: C 51.0; H 4.3; Br 17.9; N 12.5; S 7.2.

1,2-Dimethyl-3-dimethylaminomethyl-5-methoxy-6-bromoindole Hydrochloride (Va). To a solution of 2.5 g (0.01 mole) of (IIa) in 8 ml of dioxane was added a 25% aqueous solution of dimethylamine [1.4 g (0.017 mole) in 6 ml of water] and 0.5 g (0.017 mole) of 40% aqueous formaldehyde. The mixture was stirred at room temperature for 1.5 h, and the solid which separated was filtered off, washed with acetone, and dried to give 2.5 g (65.8%) of (Va), mp 266-267°C (from methanol). Found, %: C 48.35; H 5.81; Br 22.58; Cl 10.23; N 7.75. $C_{14}H_{20}BrClN_2O$. Calculated, %: C 48.36; H 5.80; Br 22.98; Cl 10.2; N 8.06.

1-Phenyl-2-methyl-3-cyanomethyl-4,5-dimethoxy-6-bromoindole (VI). To a solution of 1.52 g (0.004 mole) of 1-phenyl-2-methyl-3-dimethylaminomethyl-4,5-dimethoxy-6-bromoindole (Vc) [2] in 50 ml of dioxane was added 2.3 g (0.016 mole) of iodomethane. The mixture was stirred for 0.5 h at 15-20°C, the solid filtered off, washed with dioxane, and dissolved in 50 ml of dioxane. To this solution was added 0.2 g (0.004 mole) of sodium cyanide dissolved in 2 ml of water. The mixture was boiled for 3.5 h, then diluted with 150 ml of water, and the solid which separated was filtered off, washed with water, dried, and recrystallized from alcohol

to give 1.3 g (90%) of (VI), mp 105-107°C. Found, %: C 59.3; H 4.7; Br 21.1; N 6.9. $C_{19}H_{17}BrN_2O_2$. Calculated, %: C 59.2; H 4.5; Br 20.7; N 7.3.

EXPERIMENTAL BIOLOGICAL PART

The antiviral activity of the compounds was examined using influenza A virus (strain A/FPV (H7N7) and A/Bethesda/63 (H_2N_2).

The viral inhibitory activity of the compounds was examined in a primarily trypsinized culture of chick embryo fibroblasts (CEF) infected with 10–100 TCD_{50} of the virus. The maximum tolerated dose (MTD) of the compounds in CEF was established in preliminary experiments. This was 20 μg/ml for (IIIc), (IVc), and (VI), and 10 μg/ml for (IIIa), (Va), (IIa), and (IIb The antiviral activity of the compounds was examined using concentrations of 1/4 and 1/8 of the MTD. The virus inhibitory activity of the compounds was assessed by the prevention of the cytopathic effects of the virus of the cells, and by the reduction (expressed as a percentage) in the numbers of platelets in the test flasks as compared with the controls.

The therapeutic activity of the compounds was examined in a model of influenzal pneumonia, induced by intranasal infection of the animals with influenza virus. The infective dose of the virus was 10 LD_{50}, causing the deaths of 80-90% of the mice in the control groups The test compounds were administered to the mice in doses of 125 and 62.5 mg/kg (1/4 and 1/8 of the MTD) in prophylactic therapeutic mode (one hour before infection and then daily for four days). The activity was assessed by the reduction in deaths from influenza pneumonia (as a percentage), and by the increase in the average lifespan of the animals in the treated as compared with the control groups.

It was found that (IIa), (IIb), (IIIa), and (IVc) possessed inhibitory activity on the reproduction of the influenza virus in a culture of CEF. The highest activity was shown by (IIa) and (IIb), which in concentrations of 2.5 μg/ml reduced the numbers of platelets in the test flasks by 50-70% over the controls ($P < 0.01$). Compounds (IIIa) and (IVc) were less active, inhibiting viral platelet formation by 30-40% in concentrations of 2.5-5 μg/ml ($P < 0.05$). It is, however, noteworthy that the chemotherapeutic index (the ratio of the minimum active concentration of the compound to the maximum tolerated by the cell culture) was no greater than four for any of the active compounds.

None of the test compounds showed any activity in the model influenzal pneumonia in mice

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