The duration of the effect of the propanilide VI was closely related to the dose and varied from 15 minutes (10 mg/kg) to 1 hour (25 mg/kg). A biological study of both the δ-isomer and a mixture of the δ- and γ-isomers of compound VI showed that neither the acute toxicity nor the general character of activity nor the effectiveness of analgesic activity varied between isomers.

A comparison shows that the propanilide VI was a less effective pain reliever than promedol, morphine, and fentanyl in all the tests.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF AMINOMETHYL DERIVATIVES OF 4-HYDROXY-5-METHOXYINDOLE

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During the course of a search for compounds with antiviral activity, the 2-, 3-, and 7-aminomethyl derivatives of 1-phenyl-2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromoindole [1] have been synthesized.

The hydroxy group in compound I was protected by acetylation with acetic anhydride, giving the O-acetyl derivative (II), which on bromination with N-bromosuccinimide was converted to the 2-promomethyl derivative (III). Treatment of III with isopropylamine gave 1-phenyl-2-isopropylaminomethyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromoindole (IV), which was isolated as the hydrochloride.

Aminomethylation of compound I gave the 7-aminomethyl derivatives 4-hydroxy-5-methoxyindole (V, VI), also isolated as the hydrochlorides.

Hydrolysis of compound I with alcoholic base gave the 3-carboxylic acid (VII), which on refluxing in glycol was converted to 1-phenyl-2-methyl-4-hydroxy-5-methoxy-6-bromoindole (VIII): Methylation of the latter with dimethyl sulfate in the presence of potassium hydroxide gave 1-phenyl-2-methyl-4,5-dimethoxy-6-bromoindole (IX). Aminomethylation of IX with formaldehyde and dimethylamine hydrochloride gave 1-phenyl-2-methyl-3-dimethylaminomethyl-4,5-dimethoxy-6-bromoindole (X).

The antiviral properties of compounds I, IV-VII, and X were studied. The 3-aminomethyl derivative X exhibited pronounced antiviral activity against influenze type A virus in *in*

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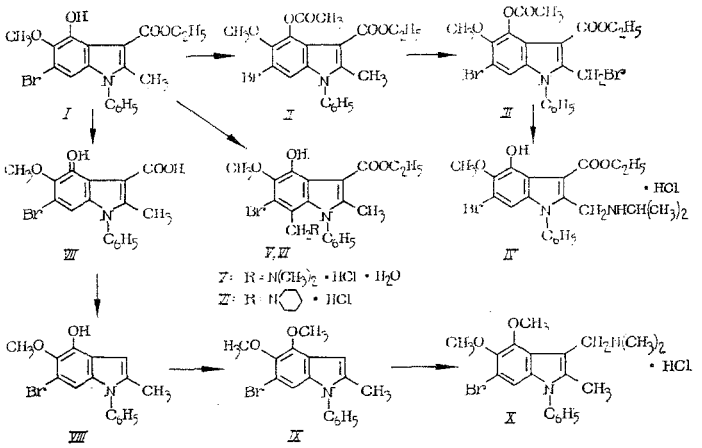
vitro tests. However, *in vivo* tests on mice with influenzal pneumonia showed this compound to be inactive.



EXPERIMENTAL CHEMISTRY

1-Phenyl-2-methyl-3-carbethoxy-4-acetoxy-5-methoxy-6-bromoindole (II). A mixture of 5.4 g (0.013 mole) of I, 20 ml of acetic anhydride, and 3 drops of concentrated sulfuric acid was heated at 70°C with mixing for 5 hours, and then diluted with water. The precipitated material was filtered off, washed with water, and recrystallized from alcohol to give 5.8 g (98%) of II with mp 165-7°C. Found, %: C 56.33; H 4.67; Br 18.32; N 3.00. $C_{21}H_{20}BrNO_5$. Calculated, %: C 56.51; H 4.52; Br 17.91; N 3.14.

1-Phenyl-2-bromomethyl-3-carbethoxy-4-acetoxy-5-methoxy-6-bromoindole (III). A mixture of 5.8 g (0.013 mole) of II, 2.34 g (0.013 mole) of N-bromosuccinimide, and 12 ml of carbon tetrachloride was refluxed for 10 hours in the presence of benzoyl peroxide. The precipitated succinimide was filtered from the hot reaction mixture, the solvent evaporated and the residue recrystallized from carbon tetrachloride to give 3.3 g (49%) of III with mp 181-2°C. Found, %: C 47.73; H 3.33; Br 29.96; N 2.50. $C_{21}H_{19}Br_2NO_5$. Calculated, %: C 48.02; H 3.65; Br 30.43; N 2.67.

1-Phenyl-2-isopropylaminomethyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromoindole Hydrochloride (IV). To a solution of 3.3 g (0.006 mole) of III in 30 ml of benzene was added 1.06 g (0.018 mole) of isopropylamine, the reaction mixture left for 24 hours at room temperature, and then washed with water. The benzene layer was separated off and evaporated to dryness. The residue was dissolved in acetone, ethereal hydrogen chloride added, and the precipitated hydrochloride filtered off. A yield of 0.8 g (27%) was obtained, mp 224-6°C (with decomposition; from alcohol). Found, %: C 54.02; H 5.61; Br 16.87; Cl 7.03. $C_{22}H_{26}BrClNO_4$. Calculated, %: C 54.61; H 5.42; Br 16.52; Cl 7.33; N 2.90.

1-Phenyl-2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromo-7-dimethylaminomethylindole Hydrochloride (V). A mixture of 4.04 g (0.01 mole) of I and 6.84 g (0.06 mole) of bis(dimethylamino) methane in 50 ml of dioxane was refluxed for 70 hours and diluted with water. The precipitated material was filtered off, washed with water, dried, and dissolved in ether. Addition of ethereal hydrogen chloride gave 2.4 g (46%) of the hydrochloride, mp 189-191°C (with decomposition; from water). Found, %: C 51.35; H 5.64; Br 15.86; Cl 7.04; N 5.57; H_2O 3.58. $C_{22}H_{26}BrClN_2O \cdot H_2O$. Calculated, %: C 51.22; H 5.47; Br 15.49; Cl 6.87; N 5.43; H_2O 3.50.

1-Phenyl-2-methyl-3-carbethoxy-4-hydroxy-5-methoxy-6-bromo-7-piperidinomethylindole Hydrochloride (VI). A mixture of 2 g (0.005 mole) of I, 1.7 g (0.02 mole) of piperidine, 0.7 ml (0.01 mole) of 37% aqueous formaldehyde, and 30 ml of dimethylformamide was refluxed for 16 hours, then diluted with water. The precipitated material was filtered off, washed with water, and dried. Treatment as for V gave 1 g (38%) of VI with mp 183-5°C (with decomposition; from acetone). Found, %: C 55.90; H 5.56; Br 14.60; Cl 6.20; N 5.32. $C_{25}H_{26}BrClN_2O_4$. Calculated, %: C 55.82; H 5.62; Br 14.86; Cl 6.59; N 5.21.

1-Phenyl-2-methyl-4-hydroxy-5-methoxy-6-bromoindole-3-carboxylic Acid (VII). To a refluxing solution of 18.5 g (0.33 mole) of sodium hydroxide in 300 ml of alcohol was added 13.4 g (0.033 mole) of I. This suspension was refluxed for 5 hours and the solvent evapo-

rated. The residue was dissolved in water, acidified with hydrochloric acid, and the precipitate filtered off to give 9.6 g (77%) of VII with mp 193-5°C (with decomposition; from methanol). Found, %: C 53.63; H 3.69; Br 20.92; N 3.57. $C_{17}H_{14}BrNO_4$. Calculated, %: C 54.27; H 3.75; Br 21.24; N 3.72.

1-Phenyl-2-methyl-4-hydroxy-5-methoxy-6-bromoindole (VIII). A solution of 12.5 g (0.033 mole) of VII in 100 ml of glycol was refluxed for 1 hour and diluted with water. The precipitated material was filtered off and chromatographed on a silica gel column using benzene as eluant to give 9.4 g (85%) of VIII with mp 134-136°C (from petroleum ether). Found, %: C 57.80; H 4.29; Br 29.93; N 4.13. $C_{16}H_{14}BrNO_2$. Calculated, %: C 57.85; H 4.25; Br 24.05; N 4.22.

1-Phenyl-2-methyl-4,5-dimethoxy-6-bromoindole (IX). To a solution of 3.3 g (0.01 mole) of VIII in 30 ml of acetone was added 1.4 g (0.01 mole) of anhydrous potassium carbonate. The reaction mixture was refluxed for 40 minutes, dimethyl sulfate 2.5 g (0.02 mole) added and refluxing continued for 10 hours. The solid material was filtered off, the filtrate evaporated to dryness, and the residue recrystallized from acetone to give 2.8 g (81%) of XI with mp 138-140°C. Found, %: C 59.06; H 4.61; Br 23.15; N 4.22. $C_{17}H_{16}BrNO_2$. Calculated %: C 58.97; H 4.66; Br 23.08; N 4.05.

1-Phenyl-2-methyl-3-dimethylaminomethyl-4,5-dimethoxy-6-bromoindole (X). A mixture of 4.8 g (0.014 mole) of IX, 1.7 g (0.02 mole) of dimethylamine hydrochloride, 5 ml of water, 1.5 ml (0.02 mole) of 37% aqueous formaldehyde, and 55 ml of isopropyl alcohol was refluxed for 7 hours. The solvent was evaporated and the residue recrystallized from alcohol to give 3 g (49%) of X with mp 220-220.5°C. Found, %: C 54.47; H 5.40; Br 18.46; Cl 8.19; N 6.24. $C_{20}H_{24}BrClN_2O_2$. Calculated, %: C 54.62; H 5.50; Br 18.17; Cl 8.06; N 6.37.

EXPERIMENTAL BIOLOGY

The antiviral activity of compounds I, IV-VII, and X on influenze type A strain A/PR 8/34 (HON1), A/Bethesda/63(H2N2) virus was studied.

The antiviral action of the compounds was studied by the following method: equal volumes of solutions or suspensions of the test substances at various concentrations were mixed with 10 and 100 50% infective doses (ID_{50}) of virus. The mixture was maintained for 1 hour at 14°C and then injected into the allantoic cavity of 9-day-old chick embryos in 0.2 ml quantities. After 48 hours incubation at 37°C, the activity of the compounds in the allantoic liquid was determined by the method of hemogluttination titration. The activity of the substances was expressed as the quantity of neutralized influenza virus.

Chemotherapeutic activity was studied on mice with influenzal pneumonia. Test compounds were administered orally to nonpedigree white mice weighing 18-20 g, 1 hour before intranasal infection with influenza virus; maximum tolerable and minimum doses were given for 4 days. Chemotherapeutic activity was evaluated over 14 days of observations; numbers of surviving mice in test and control groups were compared.

Of the compounds studied, compound X exhibited pronounced antiviral activity: At a concentration of 1 mg/ml it decreased the viral titer in comparison with the control by 3 log ID_{50} and at a concentration of 0.1 mg/ml by 1 log ID_{50}. Compound X showed no chemotherapeutic action on viral pneumonia in mice.

These results indicate that the search for antiviral compounds among aminoalkyl derivatives of 4-hydroxy-5-methoxyindole shows promise.