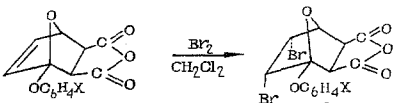
ANTIVIRAL ACTIVITY OF ADDUCTS OF ARYL- AND ARYLOXYFURANS WITH ESTERS OF ACETYLENE DICARBOXYLIC ACID, MALEIC ANHYDRIDE, AND N-PHENYLMALEIMIDE

I. S. Nikolaeva, T. V. Pushkina,
G. N. Pershin, A. F. Oleinik,
E. V. Adamskaya, and E. A. Golovanova

UDC 615.281.8.012.1

It was previously shown by us [1], that adducts of aryl- and aryloxyfurans with esters of acetylene dicarboxylic acid, maleic anhydride, and N-phenylmaleimide and also the products of their aromatization, possess tuberculostatic activity *in vitro*.

The antiviral activity of these compounds has been studied in the present work. Further, we have synthesized and studied the antiviral activity of bromine substituted adducts of aryloxyfurans and maleic anhydride. Bromination of the anhydrides of 3-aryloxy-3,6-endoxo-3,6-dihydrophthalic acid (Ia, b) was carried out in a solvent of low polarity which, according to literature data for the adduct of unsubstituted furan with maleic anhydride [2], aided the formation of cis-dibromides (IIa,b).



I a) X=H
b) X=CH3

IIa,b

Study of the antiviral activity of substances was carried out in relation to influenza A viruses [strains A/PR8/34 (HONI), A/Bethesda/63 (H_2N_2)] and type 1 herpes simplex virus (strain 1-C).

The virucidal action of compounds on influenza virus was studied by mixing definite volumes of solutions or suspensions of them of various concentration with different amounts (1-100) of a 100% embryonal infective dose (EID_{100}) of virus. Mixtures were kept for 1 h at 14°C and injected in a volume of 0.2 ml into the allantoic cavity of 9 day chick embryos. After 48 h incubation in a thermostat at 37°C the influenza virus titer was determined in the allantoic fluid with the aid of the hemagglutination reaction. The activity of substances was expressed as the amount of neutralized EID_{100} of influenza virus. The chemotherapeutic activity of compounds was studied on a viral pneumonia model in mice. The studied compound was injected into mice weighing 18-20 g 1 h before intranasal administration of influenza virus and also on the following days at the maximum tolerated and at lower doses. Chemotherapeutic activity was assessed on the basis of a comparison of survival in experimental and control groups of mice. The virus inhibitory action of substances on herpes simplex virus was studied in a primary cell culture of chick embryo fibroblasts (CEF). Substances were placed at the maximum tolerated and at lower concentrations in test tubes with a cell monolayer during 1.5 h after infection of the monolayer with various amounts (1-100) of the 50% tissue cytostatic dose (TCD_{50}) of virus. The absence of the cytostatic action of the virus on cells served to assess the virus-inhibiting action of substances.

It was established by us that of 11 substances studied which were synthesized by us previously [1] and were adducts of aryl- and aryloxyfurans with acetylene dicarboxylic acid esters, maleic anhydride, and N-phenylmaleimide, and also products of their aromatization, only two compounds, the dimethyl ester of 3-(p-acetylaminophenyl)-6-hydroxyphthalic acid [3] and 3-(p-hydroxyphenyl)-6-hydroxyphthalic acid [3] proved to have weak virucidal action on influenza virus, partially reducing the infective properties of 1 EID_{50} at a concentration of 1000 μg/ml

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 8, pp. 50-51, August, 1981. Original article submitted December 24, 1980.

0091-150X/81/1508-0567$07.50

and one compound viz. 3-(p-tolyloxy)phthalic anhydride [1], at a concentration of 10 μg/ml inhibited the multiplication of herpes virus on inoculation of a cell culture of CEF with 10 TCD_{50} of virus.

On studying the bromine substituted adducts of aryloxyfurans with maleic anhydride (IIa, b) which were synthesized in the present work, it was established that these compounds proved to have virucidal action on influenza virus. A concentration of 1000 μg/ml neutralized 1 EID_{100} of virus. Weak inhibitory action on herpes virus was shown only by substance (IIa), which at concentrations of 10 and 5 μg/ml reduced the multiplication of virus on inoculation of CEB cultures with 1 TCD_{50}.

The studied compounds showed no therapeutic action on viral pneumonia.

The carried out investigations have made it possible to show the antiviral activity of brominated adducts of aryloxyfurans with maleic anhydride and of some derivatives of aryl- and aryloxyphthalic acid in relation to influenza and herpes simplex viruses.

EXPERIMENTAL (CHEMICAL)

3-Phenyloxy-3,6-endoxo-4,5-dibromohexanhydrophthalic Anhydride (IIa). A solution of bromine (4 g: 25 mmole) in methylene chloride (5 ml) was added dropwise with stirring to a suspension of (Ia) (6.3 g: 25 mmole) in methylene chloride (30 ml) which was cooled to −20°C. The reaction mixture was stirred for 3 h at −20°C. Hexane was added to the resulting solution until completion of separation of a precipitate. The isolated crystals were filtered off and recrystallized from carbon tetrachloride. Compound (IIa) (4.4 g: 44%) was obtained of mp 153-154°C (with decomposition). Found, %: C 40.3; H 2.4; Br 38.1. $C_{14}H_{10}Br_2O_5$. Calculated, %: C 40.2; H 2.4; Br 38.2.

3-(p-Tolyloxy)-3,6-endoxo-4,5-dibromohexahydrophthalic Anhydride (IIb). Compound (IIb) was obtained in a similar manner to the previous experiment. Yield was 50%, mp 165-8°C (with decomposition). Found, %: C 41.7; H 2.8; Br 36.8. $C_{15}H_{12}Br_2O_5$. Calculated, %: C 41.7; H 2.8; Br 37.0.

LITERATURE CITED

1. A. F. Oleinik, E. V. Adamskaya, K. Yu. Navitskii, et al., Khim.-Farm., Zh., No. 3, 49-53 (1980).
2. J. Berson and R. Swidler, J. Am. Chem. Soc., 76, 4060-4069 (1954).
3. A. F. Oleitskii, E. V. Adamskaya, K. Yu. Novitskii, et al., Khim. Geterosikl. Soedin., No. 1, 17-20 (1979).