SYNTHESIS AND ANTIVIRAL ACTIVITY OF ESTERS OF PHENYLHYDRAZONO-2,7-DIHYDROXY-9-FLUORENONES

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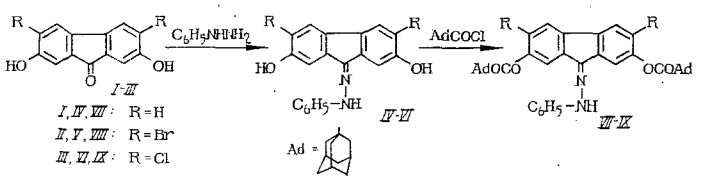
It is known [1-3] that fluorenone derivatives have a high biological activity, including antiviral activity. They stimulate the formation of interferon in experimental animals and are active with respect to a wide range of RNA- and DNA-containing viruses [4]. It has already been reported [5] that the most active compound in this group is 2,7-bis-[(2-diethylamino)ethoxy]9-fluorenone (tylorone). Data on the pharmacological tests of tylorone analogs showed good prospects for the search for effective preparations in this series.

The present article deals with the synthesis of new fluorenone derivatives containing phenylhydrazone and adamantane fragments in the molecule and study of the relationship between their structure and biological activity. Interest in this type of compounds was aroused by the fact that hydrazones exhibit a high biological, in particular, antiviral activity [6], and the introduction of the adamantyl residue increases the lipophilic character of these compounds [7].

Esters of phenylhydrazono-2,7-dihydroxyfluorenones were obtained by using the Einhorn acid chloride method [8].

The above compounds were synthesized by the following scheme:



The starting materials for the synthesis of the compounds shown in the above scheme are 2,7-dihydroxy-9-fluorenone and its 3,6-dihalo derivatives [5]. Compounds IV-VI were synthesized by the reaction between I-III, in turn, with phenylhydrazine in an alcoholic solution, with heating. Compounds VII-IX were obtained by acylation of phenylhydrazones IV-VI with adamantantanoyl chloride in pyridine. Compounds VII-IX were purified by chromatography on silica gel.

The structure of compounds VII-IX synthesized was confirmed by the data of IR spectroscopy. In the IR spectrum of these compounds there are absorption bands in the 1750-1740 cm^{-1} region (ester C=O), 1650-1600 cm^{-1} (C=N), 3380 cm^{-1} (NH), 2960-2840 cm^{-1} (C–H), 770 cm^{-1} (C–Cl), 780 cm^{-1} (C–Br).

The antiviral activity of compounds VII-IX was studied on growing chicken embryos; it was found that the value of the protection index of the A[2]Leningrad influenza virus is 20-35%.

EXPERIMENTAL

The IR spectra were run on the UR-20 spectrometer (GDR) in KBr tablets. Silica gel 40/100 (CSSR) was used for the column chromatography. The column was 50 cm long and 1.5 cm in diameter. Benzene was used as the eluent. The identity of the compounds was confirmed by TLC in a benzene–chloroform–methanol (5:3.5:1.5) system on Silufol UV-254 plates (Czechoslovakia).

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Phenylhydrazone of 2,7-dihydroxy-9-fluorenone (IV). A 12.8 g (0.12 mole) portion of phenylhydrazine was added to a solution of 3.4 g (0.04 mole) of I in 350 ml of ethanol. The mixture was heated, with stirring, for 4 h. At the end of this time, 12 ml of acetic acid were added, and the mixture was heated for another hour. The cooled mixture was poured into a considerable amount of water. The precipitate was filtered and recrystallized from dilute alcohol (1:1). Yield, 3.82 g (79%), mp 250-252°C. Found %: C 75.92; H 4.71; N 9.19. $C_{19}H_{14}N_2O_2$. Calculated, %: C 75.49; H 4.63; N 9.23.

Phenylhydrazone of 3,6-dibromo-2,7-dihydroxy-9-fluoroenone (V) was obtained in the same way as compound IV. Yield 63%, mp 235-237°C. Found, %: C 49.50; H 2.55; N 6.30; Br 34.39. $C_{19}H_{11}Br_2N_3O_2$. Calculated, %: C 49.58; H 2.61: N 6.09; Br 34.78.

Phenylhydrazone of 3,6-dichloro-2,7-dihydroxy-9-fluorenone (VI) was obtained in the same way as compounds IV and V. Yield 61%, mp 246-248°C. Found, %: C 61.52; H 3.30; N 7.83; Cl 18.85, $C_{19}H_{22}Cl_2N_2O_2$. Calculated, %: C 61.47; H 3.23; N 7.55; Cl 19.10.

Phenylhydrazone of 2,7-diadamantanoyloxy-9-fluorenone (VII). A 2.1 g (0.01 mole) portion of IV in 25 ml of dry pyridine was added to adamantanoyl chloride, obtained from 3.6 g (0.02 mole) of adamantanecarboxylic acid. The mixture was shaken for 30 min, and then left to stand for 10 h. The reaction product was poured into water. The precipitate was filtered, washed with water, and purified by column chromatography. Yield 3.3 g (55%) of VII in the form of yellow crystals, mp 301-303°C. Found, %: C 79.00; H 7.25; N 4.63. $C_{41}H_{42}N_1O_4$. Calculated, %: C 78.60; H 6.91: N 4.47.

Phenylhydrazone of 3,6-dibromo-2,7-diadamantanoyloxy-9-fluorenone (VIII) was obtained in the same way as compound VII. Yield 60%, mp 346-348°C. Found, %: N 4.00; Br 20.69. $C_{41}H_{40}Br_2N_2O_2$. Calculated, %: N 4.03; Br 20.40.

Phenylhydrazone of 3,6-dichloro-2,7-diadamantanoyloxy-9-fluorenone (IX) was obtained in the same way as compouds VII and VIII. Yield 49%, mp 380-382°C. Found, %: N 3.75; Cl 9.80. $C_{41}H_{40}Cl_2N_2O_4$. Calculated, %: N 4.03; Cl 10.21.

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