Chemistry of Natural Compounds, Vol. 31, No. 1, 1995

WATER-SOLUBLE ACETYLCELLULOSE AS A BASIS FOR THE CREATION OF ANTIVIRAL SUBSTANCES AND INTERFERON INDUCTORS

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UDC 576.858.095.393

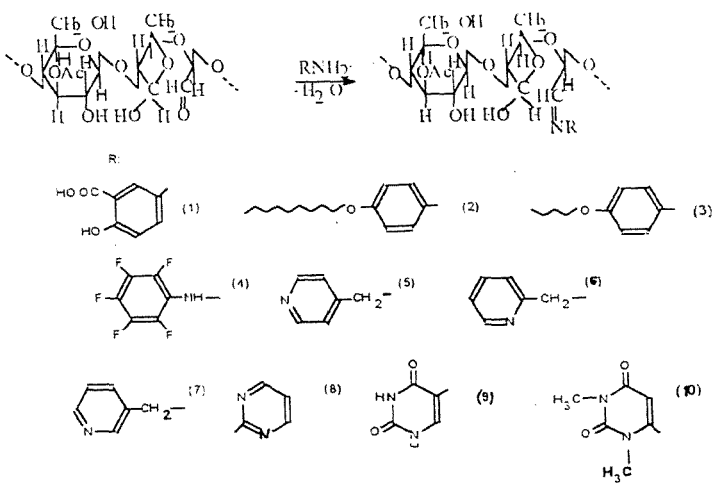
New derivatives of the benzene, pyridine, and pyrimidine series have been synthesized from the oxidized form of water-soluble acetylcellulose (WSAC), and their toxicity and antiviral activity have been studied in cell cultures. The presumed structure of the compounds synthesized has been investigated with the aid of physicochemical methods of analysis.

The possibility of using WSAC in the synthesis of substances possessing antimicrobial, antitumoral, and antiviral activities has been shown previously [1, 2]. The introduction of aldehyde groups into the WSAC molecule is a good basis for performing various modifications of directed nature.

The aim of the present work was to synthesize, determine the structure, and study the biological activity of new derivatives of water-soluble forms of cellulose.

The WSAC was synthesized from cellulose diacetate (DAC) by partial acid hydrolysis [3]. Under the action of periodic acid on the WSAC molecule the bond between C_2 and C_3 of the pyran ring is cleaved and hydroxy groups are oxidized with the formation of aldehydes [4].

The synthesis of the new OWSAC derivatives was effected by the following scheme:



The physicochemical characteristics of the compounds synthesized are given in Table 1.

The results of a study of the toxicity and antiviral activity of the compounds synthesized in a culture of chick embryo fibroblasts (CEFs) showed that they were substances with a low toxicity. The maximum acceptable dose on contact of the preparations with the CEF culture for 24 h was more than 2500 μg/ml and changed only slightly for different radicals.

Tashkent State University, fax (3712) 46 24 72. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 165-167, January-February, 1995. Original article submitted October 17, 1994.

0009-3130/95/3101-0138$12.50

TABLE 1

Compound	Yield, %	[η]	IR −C=N−, cm^{-1}	UV λ_{max}, nm
1	95.7	0.814	1642	300
2	95.0	0.805	1645	230, 300
3	92.8	0.754	1644	235, 300
4	75.6	0.720	1645	262
5	89.5	0.686	1640	258
6	91.2	0.642	1638	260, 300
7	90.9	0.615	1640	260
8	89.5	0.800	1645	230
9	99.3	0.860	1640	287
10	90.2	0.900	1680	265

The antiviral activity of the majority of compounds synthesized in a culture of CEF cells in relation to the vesicular stomatitis virus (VSV) was shown at a concentration 2-3 times lower than the toxic dose, at 1000-1600 μg/ml. The OWSAC derivative containing a 3-carboxy-4-hydroxyaniline residue (compound **1**) possessed a comparatively high antiviral activity — the minimum dose showing activity was 250-300 μg/ml.

The water solubility of the compounds synthesized and their manifestation of antiviral activity in low concentrations (particularly compound **1**) make them promising material for further investigations.

EXPERIMENTAL

The IR spectra of the compounds synthesized were taken on a Specord instrument (GDR) in the form of tablets with KBr, and UV spectra on a SF-16 instrument with water as solvent. The viscosities of the compounds synthesized were determined in an Ubbelohde viscometer. Before the measurements the solutions were passed through a No. 3 Schott funnel. The characteristic viscosity was found by the graphical extrapolation of the dependence of η_{red} on the concentration.

Production of Oxidized Water-soluble Acetylcellulose. After the complete dissolution of 10 g (0.05 mole) of WSAC in 100 ml of water, 7 g (0.03 mole) of periodic acid was added, and the mixture was stirred at 25°C for 65 min. After the lapse of the given time, the solution was precipitated in acetone. The precipitate was dried in the air. Yield 9.3 g (93.0%). $[\eta] = 0.70$.

Preparation of 4-O-4-O-(3-O-Acetyl-O-D-glucopyranosyl)-(D-glucopyranosyl)-2-O-(3-O-3-carboxy-4-hydroxyaniliniminoglyoxyl-D-erythrose)-D-glucose (1) [sic]. After the complete dissolution of 0.4 g (0.002 mole) of WSAC in 10 ml of water, the pH of the solution was brought to 4-5 with 0.5% acetic acid. At 38-40°C, with constant stirring, 0.060 g (0.0004 mole) of 3-carboxy-4-hydroxyaniline was added. The reaction mixture was stirred for 2.5 h, and the product was then precipitated in acetone. To eliminate unchanged amine the precipitate was washed several times with acetone and was dried in the air. Yield 0.383 g (95.7%). $[\eta] = 0.814$.

The WPAC derivatives (**2-10**) were synthesized analogously, with 4-nonyloxyaniline, 4-butoxyaniline, pentafluorophenylhydrazine, 4-methylaminopyridine, 2-methylaminopyridine, 3-methylaminopyridine, 2-aminopyrimidine, 5-aminouracil, and 1,3-dimethyl-4-aminouracil, respectively.

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