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Abstract

Full Text

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On the Synthesis of the *p*-Aminosalicylic Ester of Polyvinyl Alcohol

In recent decades, hundreds of new preparations have been synthesized and tested for the treatment of tuberculosis; however, it has turned out that, in terms of therapeutic action, none of them can replace streptomycin, phthivazide, and PASA ([1]). Therefore, at present the principal method of treating tuberculosis is combined treatment with streptomycin or phthivazide in combination with PASA.

PASA—*p*-aminosalicylic acid, the first synthetic preparation to find wide use in the treatment of tuberculosis. Its principal drawback is its very rapid elimination from the patient' s organism ([2]): 10 hours after administration, as much as 60-80% of the administered PASA is excreted with the urine ([3]). Therefore, in order to maintain a bacteriostatic concentration of PASA in the blood, it is necessary to give it to patients up to 15-20 g per day, which amounts to as much as 1.5-2 kg per course of treatment ([4]). Naturally, the introduction into the patient' s organism of such a large quantity of a chemical preparation causes numerous side reactions ([5]). Therefore chemists throughout the world are faced with the task of modifying the PASA molecule in such a way that, while preserving its therapeutic activity, the rate of elimination of the preparation from the organism is reduced ([4]).

In the present work, an attempt was made to modify the properties of PASA according to the general method described by one of us for modifying organic medicinal compounds by incorporating them into the structure of the macromolecule of a synthetic polymeric blood substitute ([6]), with the aim of using the preparation for administration into the blood (as well as subcutaneously and intramuscularly). Polyvinyl alcohol was used by us as such a polymer.

Since it is known that esterification of the carboxyl group ([7],[8]) does not reduce the therapeutic activity of PASA, it could be assumed that the *p*-aminosalicylic ester of polyvinyl alcohol should likewise exert a bacteriostatic effect on the mycobacteria of tuberculosis.

We obtained the *p*-aminosalicylic ester of polyvinyl alcohol by esterifying polyvinyl alcohol with the acid chloride of PASA. The sodium salt of *p*-

aminosalicylic acid in the form of the dihydrate was used as the starting material. *p*-Aminosalicylic acid was precipitated from an aqueous solution of the sodium salt of PASA with a hydrochloric acid solution at pH 3 ([9],[10]). The acid chloride of *p*-aminosalicylic acid was obtained by the action of thionyl chloride ([11]) on *p*-aminosalicylic acid in an ether medium or in pyridine solution, followed by precipitation with chloroform.

The acid chloride obtained contains an admixture of the condensation product of two molecules of PASA acid chloride due to interaction of the amino and chloro groups of neighboring molecules.

Table 1.

Synthesis of *p*-aminosalicylic esters of polyvinyl alcohol

Experimental conditions	mol. AC per 100 mol. PVA	Duration of experiment, h	Treatment	Presence of chlorine	Nitrogen content, %	Ester units content, wt. %	Ester units content, mol. %	Qualitative reaction to chlorine (fusion with sodium)	PASK content, %	Intrinsic viscosity $[\eta]$*
In pyridine medium, 100°	5	5	Reprecipitated with methanol	No	0.64	0.70	7.6	2.0	+	6.5	
In pyridine medium, 100°	50	6	Reprecipitated with acetone	Yes	1.36	0.56	5.9	1.5		5.0	
In dimethylformamide solution, 100°	20	5	Reprecipitated with methanol	Yes	1.83	1.08	12.2	3.3		10.4	

Experimental conditions	mol. AC per 100 mol. PVA	Duration of experiment, h	Treatment	Presence of chlorine	Nitrogen content, %	Ester units content, wt. %	Ester units content, mol. %	Qualitative reaction to chlorine (fusion with sodium)	PASK content, %	Intrinsic viscosity $[\eta]$*
In dimethylformamide solution, 100°	20	5	Reprecipitated with methanol, extracted with pyridine	»	1.22	1.22	15.7	4.4	+	13.4	0.4
In dimethylformamide solution, 100°	20	4	Same	»	0.96	1.15	13.5	3.7		11.5	0.33
In dimethylformamide solution, 100°	20	4	» »	»	0.90	1.20	13.5	3.7		11.5	0.33
In dimethylformamide solution, 100°	20	3	» »	»	2.48	2.24	30.3	9.7		25.9	

Experimental conditions	mol. AC per 100 mol. PVA	Duration of experiment, h	Treatment	Presence of chlorine	Nitrogen content, %	Ester units content, wt. %	Ester units content, mol. %	Qualitative reaction to chlorine (fusion with sodium)	PASK content, %	Intrinsic viscosity [η]*
In dimethylformamide solution, 100°	30	4	» »	»	1.692.12	25	7.6		21.5	
In dimethylformamide solution, 100°	25	4	» »	»	2.01.86	25	7.6		21.5	
In dimethylformamide solution, 100°	30	3	» »	»	0.840.86	10.8	3.0		9.25	

* [η] of the initial polyvinyl alcohol, 0.44.

The esterification reaction of polyvinyl alcohol with PASK acid chloride was carried out in pyridine medium or in dimethylformamide solution (see Table 1). In pyridine medium the synthesis was carried out by the method usually used for obtaining polyvinyl alcohol esters ([12,13]). A weighed portion of polyvinyl alcohol, after swelling in pyridine at 30–40° for 10–20 h, was treated with fresh pyridine; then the acid chloride was added, and the reaction was conducted with stirring and heating to 100° for 6 h.

After washing with fresh pyridine, the reaction product was twice reprecipitated from aqueous solution with acetone and washed with fresh acetone and ether. Water-soluble copolymers of vinyl alcohol with the *p*-aminosalicylic ester of vinyl alcohol were obtained, with an ester-unit content of 1-2 mol. % (4-7 wt. %). The ester-unit content was calculated from the nitrogen content in the samples, determined by the Dumas micromethod (provided that chlorine was completely absent).

$$-(CH_2-CH)_m-\left(\begin{array}{c} CH_2-CH \\ | \\ O \\ | \\ CO \\ | \\ -OH \\ | \\ NH_2 \end{array}\right)_n$$

where in the first unit

$$CH_2-CH \quad \begin{array}{c} | \\ OH \end{array}$$

During esterification in dimethylformamide solution (as recommended for the synthesis of cellulose esters ([14])), a considerably higher degree of esterification was achieved. To a weighed portion of polyvinyl alcohol (PVA), dissolved in dimethylformamide with heating to 130°, a solution of PASK acid chloride (AC) in dimethylformamide was added, and the reaction was conducted with stirring for 5 h at 100°.

From the reaction mixture, the ester obtained was precipitated with methanol, extracted with pyridine in a Soxhlet apparatus, and again reprecipitated from aqueous solution with methanol. The polymer was then washed with fresh methanol and ether. At an initial molar ratio $\frac{\text{HA}}{\text{PVS}} = \frac{15}{100} \div \frac{30}{100}$, a water-soluble product was obtained with a content of ester units of 3-10 mol. % (10-30 wt. %).

Thus, we developed a basic procedure for the synthesis of this previously unknown derivative of polyvinyl alcohol.

Preliminary pharmacological tests, carried out at the Leningrad Scientific Research Institute of Tuberculosis and at Tuberculosis Dispensary No. 8 by Dr. I. M. Rabinovich, established that excretion from the animal organism (rabbits) of the preparation obtained on the basis of low-viscosity polyvinyl alcohol (~9 centipoise) occurs several times more slowly than that of the ordinary PAS preparation*, namely, PAS is detected in the organism for 10-14 days. The residence

time of the preparation in the organism can be further increased by increasing the length of the macromolecule of the p-aminosalicylic ester of polyvinyl alcohol.

When the preparation was tested *in vitro* on Petragnani medium, it exerted an antimicrobial effect on tubercle mycobacteria.

In order to improve the hematopoietic properties of the preparation obtained, instead of polyvinyl alcohol it is possible to use a copolymer of vinyl alcohol with vinylpyrrolidone.

The indicated partial esters of PAS and polyvinyl alcohol containing about 20 wt. % vinyl ester of PAS were used to obtain thixotropic gels. Such gels with a melting point of 38-40° are obtained upon cooling 5-10% solutions of the polyvinyl ester of PAS to which 2% boric acid or 3% Congo red has been added. Such gels can be used for intramuscular or subcutaneous injection.

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CITED LITERATURE

1. F. V. Shebanov, *Med. rabotnik*, 1960.
2. A. I. Kiprianov, *Ukr. khim. zhurn.*, **19**, No. 3, 239 (1953).
3. R. O. Drabkina, *Vrach. delo*, No. 10, 938 (1955).
4. M. N. Shchukina, T. P. Sycheva, *Khim. nauka i prom.*, **1**, No. 4, 419 (1956).
5. A. D. Mashkovskii, *Medicinal Compounds*, Moscow, 1957, p. 499.
6. S. N. Ushakov, *Tr. LTI im. Lensoveta*, **45**, 132 (1958).
7. I. Kh. Feldman, *Bull. Inst. Tuberculosis Acad. Med. Sci. USSR*, **1**, 9 (1950).
8. D. I. Shcherbakova, *Farmakol. i toksikol.*, **22**, 1, 80 (1959).
9. S. A. Giller, A. K. Lokenbakh, A. A. Mai, *Izv. AN LatvSSR*, No. 3, 7 (1950).
10. P. P. Parker, J. M. Smith, U. S. 2644011, 30 VI 1953.

11. F. Fujikana, K. Nakajima, V. Hitosa, *J. Pharm. Soc. Japan*, **74**, 1155 (1954).

12. H. Staudinger, K. Frey, W. Starck, *Ber.*, **60**, 2, 1782 (1927).

13. S. N. Ushakov, R. K. Gavrilina, P. A. Medvedeva, *ZhPKh*, **21**, 1118 (1948).

14. Sun Tun, V. A. Derevitskaya, Z. A. Rogovin, *Vysokomolek. soed.*, **2**, No. 5, 785 (1960).

* PAS is detected in urine by a colorimetric method using a 3% solution of $FeCl_3$.

Note: Figure translations are in progress. See original paper for figures.