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Abstract

Full Text

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ON THE COMBINATION OF PENICILLINS WITH WATER-SOLUBLE POLYMERS

Prolongation of the action of medicinal compounds and, in some cases, alteration of the nature of their effect on the organism can be achieved by the method proposed by one of us ([1]), through the chemical attachment of medicinal compounds to the macromolecules of certain polymers. The medicinal polymers thus obtained are introduced into the organism by intravenous infusion of their solutions or by injection into tissues of melts of thixotropic gels obtained from them. The residence time of the medicinal compound in the organism is regulated by the length of the polymer macromolecule. This method has been carried out for the modification of a number of medicinal compounds ([2,3]). Prolongation of the action of medicinal compounds is of particular importance for penicillins and other antibiotics.

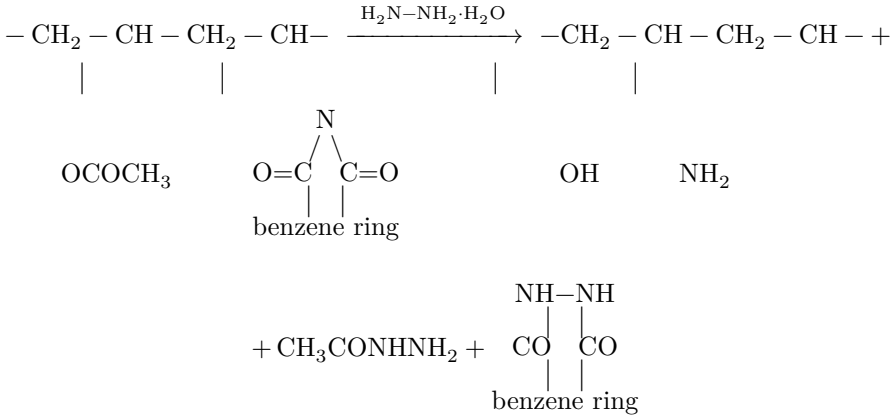
As is known, administration of penicillin by injection in the form of a suspension in vegetable oils together with wax, novocaine, etc., in order to prolong its action gives a comparatively insignificant effect. Preparations of the type of chemical (low-molecular) derivatives of penicillins with a heavier molecule also do not give the required effect. The present work was undertaken with the aim of creating a high-molecular preparation representing a chemical combination of penicillin with a polymer, variation of whose molecular weight (the length of the macromolecule) would make it possible to regulate the time of its residence in the organism. Such preparations had not been described previously. As the initial polymer possessing the appropriate properties for combination with penicillin, copolymers of vinyl alcohol and vinylamine with various contents of vinylamine units in the copolymer chain were used:

$$\begin{array}{c} -CH_2-CH-CH_2-CH-CH_2-CH- \\ \quad\quad\quad | \quad\quad\quad | \quad\quad\quad | \\ \quad\quad\quad OH \quad\quad\quad NH_2 \quad\quad\quad ON \end{array}$$

Copolymers of vinyl alcohol and vinylamine are distinguished by their solubility in water and by the stability of the solutions obtained. The copolymers were

prepared by a method developed by A. F. Nikolaev and co-workers, jointly with one of us ([4]). Preparation of the copolymers was carried out in two stages.

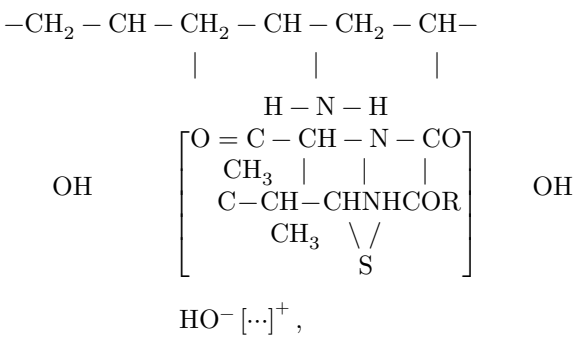
In the first stage, a copolymer of vinyl acetate and vinylphthalimide was obtained. Copolymerization was carried out in a toluene solution (50 wt.% of the weight of the comonomers) in sealed ampoules at 70°. Copolymerization was brought to a conversion of 60% (copolymer yield). The vinyl acetate, relative to vinylphthalimide, was taken in the range from 98 : 2 moles to 90 : 10 moles. In the second stage, the resulting copolymer of vinyl acetate and vinylphthalimide was treated with an excess of hydrazine hydrate. The reaction proceeds according to the following scheme:



The copolymer was heated on a water bath with a fivefold excess of hydrazine hydrate, and in the process gradually passed into solution. After completion of the reaction, which lasted 3–4 hours, the excess hydrazine hydrate was distilled off under vacuum. The resulting copolymer residue was dissolved in water and reprecipitated from the aqueous solution first with alcohol and then with acetone. The copolymer, precipitated in the form of white flakes, was washed on the filter with acetone and dried in a vacuum oven, and then in a vacuum desiccator over P_2O_5 to constant weight (since copolymers of vinyl alcohol and vinylamine readily absorb water vapor from the air).

For the subsequent reaction with penicillin the copolymer was subjected to fractionation, the low-molecular-weight fraction being discarded. The content of amino groups in the copolymer was determined by titrating an aqueous solution of a weighed portion of the copolymer with 0.01 N HCl solution, using bromophenol blue as indicator. The combination was effected by formation of the salt of penicillin (which is a strong acid) with the amino groups of the vinylamine units of the copolymer.

The content of vinylamine units in the copolymer used for combination with penicillin was $\sim$ 2 mole %. Polymers of the following salt structure were obtained:



where $R = -CH_2C_6H_5$, $-CH_2OC_6H_5$, etc.

Of the penicillin series, the most important from both a fundamental and a practical standpoint, G-(benzyl) and V-(phenoxymethyl) penicillins, were selected for study. These two penicillins differ from one another in solubility in water: penicillin G is readily soluble in water, whereas V is practically insoluble in it.

Preparation of the salt of benzylpenicillin and the copolymer of vinylamine and vinyl alcohol. The free acid was first obtained from the usual Na salt of benzylpenicillin ([5]). For this purpose, to 3 g of the Na salt of benzylpenicillin dissolved in 50 ml of water, 0.5 N HCl solution was added to pH 2-3, and the acid liberated was immediately extracted with chloroform by several successive extractions. The chloroform solution of benzylpenicillin (free acid) was added, with vigorous stirring, to an aqueous solution of 18 g of the copolymer of vinyl alcohol and vinylamine (with $[\eta] = 0.25$, determined in 0.5 M KCl solution) in 100 ml of water. An emulsion was thereby formed. When the latter was poured into acetone, the polymeric amine salt precipitated in the form of flakes; it was filtered off, washed on the filter with acetone, and dried to constant weight. The yield of the penicillin salt of the amine was 95%. The penicillin content in the copolymer was determined by the iodometric method. From calculation for 2 mole % of vinylamine units in the copolymer, the weight content of penicillin should be 13.15 wt. %. By the iodometric method 11.22% was found, corresponding to an activity of 187 units/mg. The specific rotation of the salt obtained was $[\alpha]_D^{22} + 36^\circ$ (C 3 in H_2O).

With complete substitution of all amino groups of the copolymer by penicillin, the G salt should contain (in %): N 1.66, S 1.26. Found (in %): N 1.45, S 1.10.

Preparation of the salt of phenoxymethylpenicillin and the copolymer of vinylamine and vinyl alcohol

was carried out essentially in the same way as for the salts of benzylpenicillin. However, owing to the poor solubility of phenoxymethylpenicillin in water ([6]), in this case it is possible to observe the formation of the salt directly (if, upon mixing with the copolymer solution, the penicillin dissolved, this means that a salt was formed). The solution obtained after mixing at first becomes slightly

opalescent, then becomes transparent. After complete dissolution of the penicillin, the polymer was precipitated with acetone and filtered off, washed on the filter with acetone, and dried in a vacuum desiccator over P_2O_5. The yield of the salt was 97%. The penicillin content in the copolymer was determined by the iodometric method ([7]). For complete binding of the NH_2 groups with penicillin, it proved necessary to introduce a slight excess of the latter into the reaction. Thus, with complete interaction of the vinyl alcohol–vinylamine copolymer used with V-penicillin, the content of the latter in the copolymer should be 13.7 wt.%; the iodometric method gave 13.6%, which corresponds to an activity of 270 units/mg. The specific rotation of the salt obtained was $[\alpha]_D^{21} + 35^\circ$ (c 3 in H_2O). Upon acidification of the solution to pH 2.4–2.5, phenoxymethylpenicillin precipitates.

In the case of complete replacement of all amino groups of the copolymer by penicillin, the V-salt should contain (in %): N 1.65, S 1.26. Found (in %): N 1.71, S 1.39.

The polymeric salts of penicillin obtained are rather stable compounds. They do not decompose upon dissolution in water and reprecipitation, or upon standing of the solutions. They form thixotropic gels when certain "cross-linking" substances are added to their aqueous solutions. For example, when 3% Congo red is added to a 20% solution of the polymeric salt of penicillin, a gel is formed that solidifies at a temperature of 38–39°. In the form of a melt, such a gel can be introduced into the tissues of the organism by injection with a syringe.

Preliminary biological studies (carried out at the First Leningrad Medical Institute) showed that determination of the activity of the described polymeric salts of penicillins against the standard strain of staphylococcus 209-R by the serial dilution method, in comparison with standard penicillin, gives analogous results: both the standard penicillin preparation and the polymeric salt of benzylpenicillin (recalculated to the penicillin contained in the polymer) inhibit the growth of the standard strain of staphylococcus at a concentration of 0.03 units/ml.

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

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