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Chemistry

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Abstract

Full Text

Chemistry

Corresponding Member of the Academy of Sciences of the USSR S. N. Ushakov,
E. F. Panarin

On the Synthesis of High-Molecular-Weight Amides and Hydrazides of Penicillins

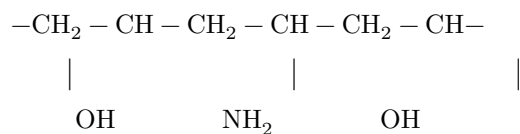
In an article ⁽¹⁾ we described a method for combining penicillins with polymers by forming salts of penicillins and copolymers of vinylamine with vinyl alcohol. In the present communication we present the results of studies undertaken with the aim of combining penicillins with the macromolecular chain of a polymer by a covalent bond. The work was carried out within the framework of developing the general problem—modification of medicinal compounds by incorporating them into the structure of certain polymers ⁽²⁾.

As starting polymers for the indicated purpose, copolymers of vinylamine and vinyl alcohol and copolymers of acrylic acid hydrazide and vinyl alcohol were used.

For the coupling, the carboxyl group of the penicillins was used, the latter being employed in the form of their mixed anhydrides with ethoxyformic acid. Coupling was carried out for the most important types of penicillins: benzylpenicillin (G) and phenoxymethylpenicillin (V).

Copolymer of vinylamine and vinyl alcohol was obtained by the described method ⁽³⁾, by copolymerizing vinyl acetate and vinylphthalimide in toluene solution in the presence of 0.5–1% benzoyl peroxide at 70° and subsequent treatment with hydrazine hydrate. After distilling off the excess hydrazine hydrate, the copolymer was reprecipitated from aqueous solution with ethanol and again —from aqueous solution with acetone.

Copolymers were obtained with a vinylamine content in the chain from 1.5 to 4 mol.% and of the following structure:

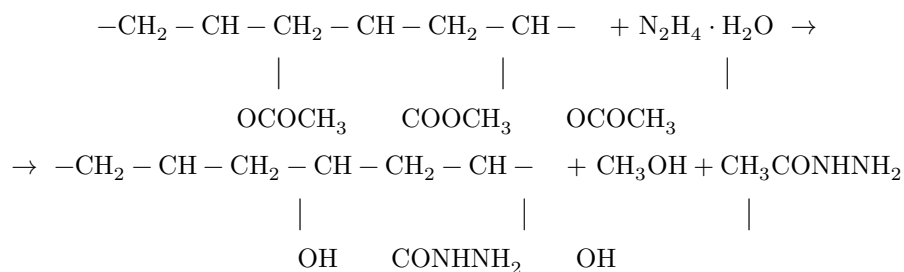


Determination of amino groups was carried out by titration with 0.01 N HCl with bromophenol blue.

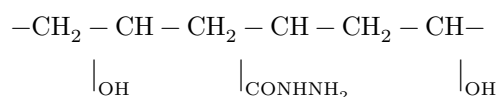
Copolymer of acrylic acid hydrazide and vinyl alcohol (apparently not previously described) was obtained in two stages.

In the first stage, copolymerization of vinyl acetate with methyl acrylate was carried out in sealed ampoules in the presence of 0.8% benzoyl peroxide, based on the weight of the comonomers, at a temperature of 70° in toluene solution. The initial mixture contained 95 mol.% vinyl acetate, 5 mol.% methyl acrylate, and 50 mol.% toluene based on the sum of the copolymers. Copolymerization was carried out for 13 hours. The yield of copolymer (with $[\eta] = 0.175$) was 73.5%.

In the second stage, the polymer obtained was treated with a fivefold excess of hydrazine hydrate on a boiling water bath for 3-4 hours until a homogeneous solution was obtained. In this process the reactions proceeded according to the scheme:



After distilling off the excess hydrazine hydrate under vacuum, the copolymer was reprecipitated three times from aqueous solution with ethanol. The copolymer contained 3.49% N, which corresponds to 5.7 mole % of acrylic acid hydrazide in the chain



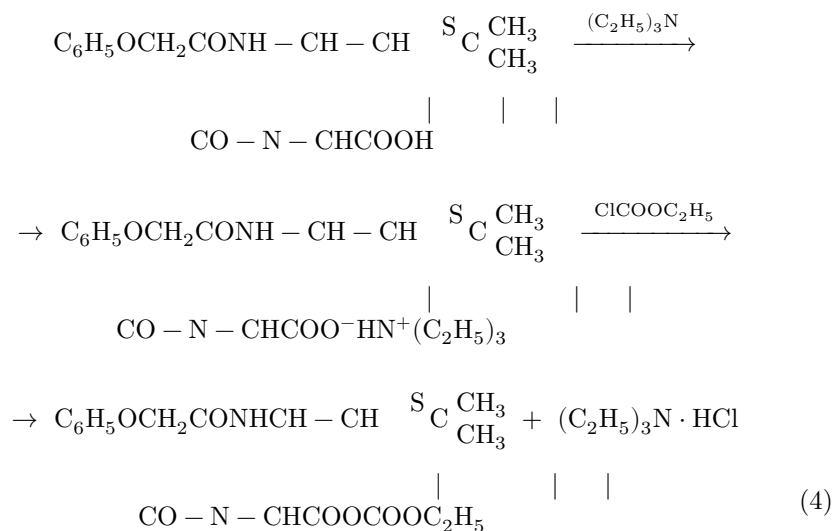
Copolymers with different contents of acrylic acid hydrazide in the chain (from 1.5 to 6 mole %) were synthesized.

The copolymer obtained is soluble in water, hydrazine hydrate, and hot dimethylformamide.

In aqueous solutions the copolymer shows an anomalous dependence of reduced viscosity on concentration and has $[\eta] = 0.37$ in a 0.5 M KCl solution at 30°.

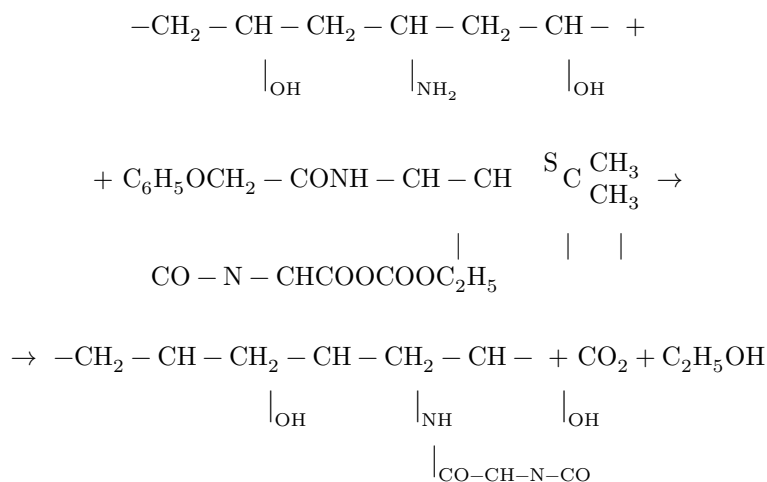
The **preparation of penicillin amides and of the copolymer of vinyl alcohol with vinylamine** was carried out by treating the copolymer with the mixed anhydride of penicillin and chloroformic ester.

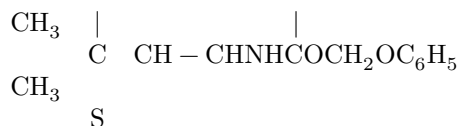
The mixed anhydride was synthesized according to scheme (4):



The reaction was carried out as follows. To a solution of 2.15 g of phenoxymethylpenicillin in 30 ml of CHCl_3 , cooled to 0° , 6.2 ml of a 1 M solution of $\text{N}(\text{C}_2\text{H}_5)_3$ in CHCl_3 was added, and after standing for 40 min at a temperature of $0 \div +5^\circ$, 6.2 ml of a 1 M solution of $\text{ClCOOC}_2\text{H}_5$ in CHCl_3 was added. After standing for one hour at $0 \div +5^\circ$, the reaction mixture was washed with cold water until the reaction for Cl' disappeared and was dried by shaking with ignited Na_2SO_4 . The resulting mixed anhydride was not isolated from the reaction mixture and was used as such for further transformations.

The polymeric amide of phenoxymethylpenicillin was obtained according to the scheme:

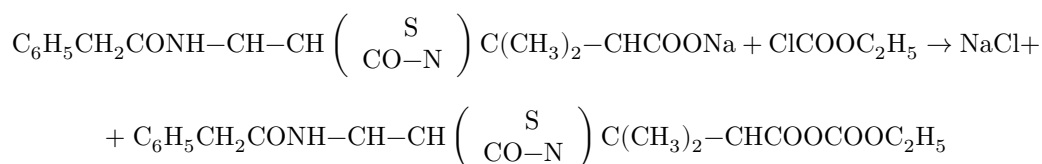




To carry out the reaction, a weighed portion of the copolymer of vinyl alcohol with vinylamine (containing 2 mol.% vinylamine), amounting to 14.4 g, was dissolved with heating in 200 ml of dimethylformamide. To the copolymer gel formed on cooling the solution to 0°, with vigorous stirring, the solution of the mixed anhydride was gradually added. The reaction was continued for 3–4 hours at 0°. The reaction product was precipitated with acetone or a mixture of acetone and ether and, after drying, was obtained in the form of a white powder (yield 90% of theory).

If the reaction proceeds completely with all amino groups in the chain of the copolymer of vinyl alcohol with vinylamine, the phenoxymethylpenicillin amide should contain (%): N 1.66, S 1.26. Found in the reaction product (%): N 1.74, S 1.35. The product is soluble in water and forms transparent solutions.

The mixed anhydride was obtained by interaction of the Na salt of benzylpenicillin with chloroformic ester according to the scheme ^(5,6):



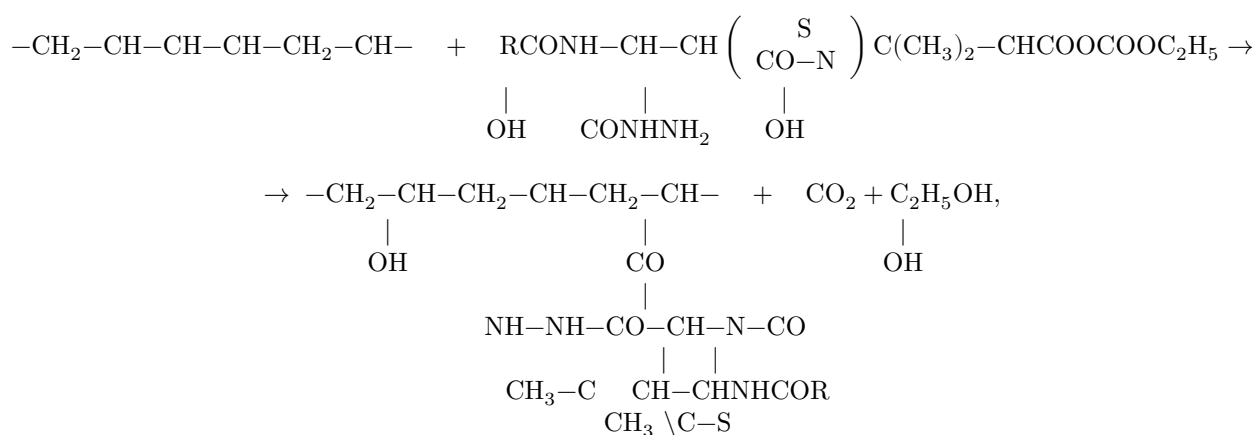
The reaction was carried out as follows. 3 g of benzylpenicillin was suspended in 30 ml of CHCl_3 , and the suspension was cooled to -5° . Then 8.5 ml of a 1 M solution of $\text{ClCOOC}_2\text{H}_5$ in CHCl_3 and 1–2 drops of pyridine were added to the suspension, and the reaction mixture was allowed to stand for 30 min at a temperature of $0 \div -5^\circ$. After the reaction was complete, the precipitated NaCl was filtered off, and the filtrate was poured into cooled petroleum ether. The mixed anhydride precipitated as a white sticky mass and was then dried under vacuum at $+5^\circ$. Yield 97% of theory. The mixed anhydride had a specific rotation $[\alpha]_D^{20} = +208^\circ$ (c 1.1 in CHCl_3).

Benzylpenicillin amide was obtained by treating the copolymer of vinyl alcohol with vinylamine with the mixed anhydride in dimethylformamide by the procedure described above. Yield 92%. The product obtained is soluble in water and contains 2.30% N and 1.71% S, which corresponds to 2.5 mol.% benzylpenicillin in the polymer.

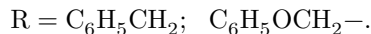
Preparation of the mixed hydrazide of penicillin and the copolymer of vinyl alcohol with acrylic acid hydrazide was carried out by treating

the copolymer with the mixed anhydride of penicillin and chloroformic ester by the procedure used for preparing the amides.

The reaction proceeds according to the scheme:



where



Copolymers containing 5.7 and 1.5 mol.% of the mixed hydrazide of penicillin and acrylic acid were obtained. The yield was 80-85% of theory. The results of temperature analysis were as follows:

	Found, % N	Found, % S	Calculated, % N	Calculated, % S	Mol. %
Hydrazide V	4.68	2.89	4.88	2.79	5.7
Hydrazide G	1.68	0.97	1.75	1.00	1.5

The copolymers form stable aqueous solutions.

Thus, for the first time, penicillins were combined with polymers possessing the properties of blood substitutes by means of a covalent bond.

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

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