STABILITY OF PENICILLINS IN AQUEOUS SOLUTIONS.
I. OXACILLIN AND PHENOXYMETHYLPENICILLIN

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The stability of phenoxymethylpenicillin and oxacillin—the sodium salt of 6-[5'-methyl-3'-phenylisoxazole-4'-carbamido] penicillanic acid—in aqueous solutions has been the subject of a number of studies [1-7]. However, the data obtained in these studies were tentative or limited to narrow ranges of pH and temperature.

In view of the continuous improvement of production and the effort to increase the quality of antibiotics, it is desirable to have data on their stability within broad ranges of pH and temperature.

An experimental study was made of the rate of inactivation of two penicillins in aqueous solutions under various conditions. Data were obtained for a calculation of the rate constant of inactivation within broad ranges of pH and temperature. This article presents the results of the investigation.

METHOD

Oxacillin, produced at the Laboratory of Organic Synthesis of the All-Union Scientific Research Institute of Antibiotics, and commercial phenoxymethylpenicillin after two crystallizations were used. The purity of the preparations was 97 and 96%, respectively. Solutions of the antibiotics in buffer mixtures with known pH were placed in water thermostats. Constancy of the temperature was maintained within limits of ±0.2°. Samples were collected from the solutions periodically and the content of undecomposed penicillin determined in them by an iodometric method [8, 9]. The data of the determinations coincided with the results of control microbiological titrings. In the preparations of the solutions we used glycine, acetate, and phosphate buffer mixtures [10]. In a study of the stability of penicillins at pH below 1.5, hydrochloric acid was used. In acid solutions, the penicillins exhibit extremely negligible solubility. Therefore, to

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Fig. 1. Course of the process of inactivation of phenoxymethylpenicillin at 35° (I) and oxacillin at 25° (II). Numbers near the straight lines—pH of solutions.

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obtain the required concentrations, we utilized the ability of the penicillins to form supersaturated solutions, stable for many hours. To prepare them, solutions of salts of the penicillins were mixed with hydrochloric acid. The concentrations of the antibiotics in the solutions comprised from 500 to 3000 µg/ml.

The process of inactivation of penicillins in aqueous solutions proceeds irreversibly according to first order for all the pH values studied. As an example, Fig. 1 presents typical results on the change in the concentration with time for oxacillin and phenoxymethylpenicillin. The data obtained are in good agreement with a linear relationship between \( \log \frac{c}{c_1} \) and \( \tau \), characteristic of irreversible first-order processes. The rate constant of inactivation of the substances (\( k \)) was calculated according to the equation

\[
k = \frac{2.303}{\tau} \log \frac{c_1}{c},
\]

where \( \tau \) is the time (in min) during which the penicillin concentration in solution changes from \( c_1 \) (initial) to \( c \).

Stability of Penicillins in Solutions as a Function of the pH. Figure 2 shows the relationship found experimentally between the logarithms of the rate constants of the inactivation of penicillins and the pH of the solutions at 25°. The curves expressing this dependence can be divided into five portions. On portion I, nondissociated molecules of the penicillins (\( PnH \)) undergo decomposition under the influence of hydrogen ions. For this portion the rate may be expressed as:

\[
-\frac{dc}{d\tau} = -\frac{dc_0}{d\tau} = kc = kc_0.
\]

where

\[
k = k_1 [H^+] \tag{2a}
\]

In the equation, \( c_0 \) is the concentration of nondissociated molecules, while \([H^+]\) is the hydrogen ion concentration.

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>( k_1 )</th>
<th>( k_2 )</th>
<th>( k_3 )</th>
<th>( n )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenoxymethylpenicillin</td>
<td>7.5 \times 10^{-2}</td>
<td>4.0 \times 10^{-2}</td>
<td>33.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>2.10 \times 10^{-1}</td>
<td>1.7 \times 10^{-1}</td>
<td>23.7</td>
<td>0.78</td>
</tr>
</tbody>
</table>

TABLE 1. Rate Constants of Inactivation of Penicillins and Exponents \( n \) at 25°