CATALYTIC REDUCTION OF 6,6-DIBROMOPENICILLANIC ACID 1,1-DIOXIDE

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We have previously reported [1] that on treatment with inorganic sulfur-containing reducing agents, 6,6-dibrompenicillanic acid 1,1-dioxide (I) undergoes partial dehalogenation to give the isomeric 6α- and 6β-bromopenicillanic acid 1,1-dioxides (IIα and IIβ).

The aim of the present investigation was to examine the reductive dehalogenation of (I) by hydrogen in the presence of a catalyst. The reduction was carried out under the conditions reported previously [2]: an 0.02 M solution of (I) was stirred at ambient temperature in a hydrogen atmosphere at a pressure of 0.3-0.5 MPa in the presence of 5% Pd/C [0.5-1.0% of the weight of (I)]. It was shown experimentally that the optimum pH range was 7.0-8.0, at which the β-lactam structure was stable, and the reaction proceeded at a satisfactory rate. The most satisfactory way of maintaining the pH during catalytic hydrogenation under pressure was by using a phosphate buffer of $NaHCO_3$ solution.

The progress of hydrogenolysis was followed by HPLC, which showed that the proportions of the components of the reaction mixture varied with the buffer solution used (Fig. 1). As will be seen from Fig. 1A, when a bicarbonate solution was used the dibromide (I) had been almost completely converted into (IIα) after 45 min, the proportion of (IIβ) being no more than 5%. During the course of the next hour the (IIα) was converted into penicillanic acid dioxide (III), i.e., hydrogenolysis of (I) in the carbonate solution was stereospecific, giving in the first step a product in which the protons at C(5) and C(6) are trans-oriented. In phosphate buffer (Fig. 1B), the formation of (IIα) is accompanied by substantial amounts of (IIβ), the isomer ratio reaching 3:1. Further hydrogenation results in the dehalogenation of (IIα) and (IIβ) to give (III), (IIβ) being dehalogenated much less rapidly than (IIα). Further, in phosphate buffer there is an increase in the amount of an impurity with a retention time of 3.0 min, evidently as a result of breakdown of the penicillin structure, thus affecting the yield of (III). It is noteworthy that if for any reason the reaction does not proceed to completion, when the reaction is carried out in hydrogen carbonate solution the (III) is accompanied by (IIα), whereas in the phosphate solution the impurity was predominantly (IIβ). It appears that the phosphate buffer stabilized (IIβ) toward catalytic dehalogenation.

Examination of the stabilities of the components of the reaction mixture showed that the initial and final products (I and III, respectively) are relatively stable both in the phosphate and the hydrogen carbonate solutions. In both cases the losses of (I) over 3 h amounted to 3-5%, and (III) remained virtually unchanged. The behavior of the monobrominated dioxides (IIα) and (IIβ) however differed. Decomposition of (IIα) in both solutions amounted to around 10%. It will be seen from Fig. 2 that the decomposition of (IIα) is an irreversible, first-order reaction. In the case of the β-isomer, the behavior is more complex, since in hydrogen carbonate solution the (IIβ) almost completely isomerizes to (IIα) in the first 20-30 min following solution (Fig. 3a). In the phosphate buffer, isomerization is much slower, since after 30 min the ratio of (IIα) to (IIβ) was 2:1, isomerization being complete within 2 h (Fig. 3b), i.e., the phosphate buffer confers some stability on the unstable configuration of the β-isomer. The plots 3 in Fig. 3a, b, showing the overall concentration of the isomers in the solutions, show that in the phosphate buffer the decomposition of the penicillin structure is more marked than in the hydrogen carbonate solution. Generally speaking, however, in the series of dioxides the stability of the monobromopenicillanic acids is lower than that of dibromopenicillanic acid.

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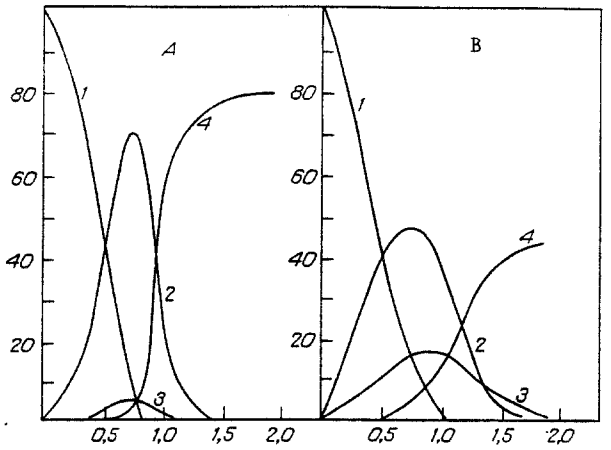

Fig. 1

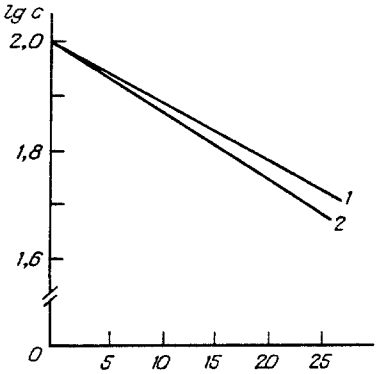

Fig. 2

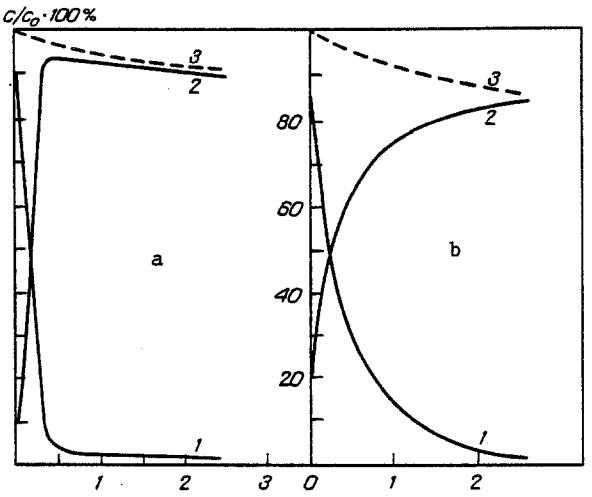

Fig. 3

Fig. 1. Composition of the reaction mixture on catalytic reduction of (I) in sodium bicarbonate solution (A) and in phosphate buffer (B): 1) 6,6-dibromopenicillanic acid 1,1-dioxide (I); 2) 6α-bromopenicillanic acid 1,1-dioxide (IIα); 3) 6β-bromopenicillanic acid 1,1-dioxide (IIβ); 4) penicillanic acid 1,1-dioxide (III). Horizontal axis – t (h); vertical axis – $(c/c_0)\cdot 100$ (%), where c and c_0 are the molar concentrations of (I), (IIα), (IIβ), and (III), respectively, at time t and at the beginning of the reaction.

Fig. 2. Decomposition of 6α-bromopenicillanic acid 1,1-dioxide (IIα) in sodium hydrogen carbonate solution (1) and in phosphate buffer (2). Horizontal axis – t (h); vertical axis – log c, where c is the molar concentration of (IIα).

Fig. 3. Isomerization of 6β-bromopenicillanic acid 1,1-dioxide (IIβ) to 6α-bromopenicillanic acid 1,1-dioxide (IIα) in sodium hydrogen carbonate solution (a) and in phosphate buffer (b). 1) (IIβ); 2) (IIα); 3) (IIβ + IIα). Horizontal axis – time (t, h); vertical axis – $(c/c_0)\cdot 100$ (%), where c and c_0 are the molar concentrations of (IIα) and (IIβ) at time t and the beginning of the reaction, respectively.

This work has thus shown that the catalytic hydrogenation of (I) to (III) takes place via the intermediate formation of (IIα) and (IIβ), the particular isomer formed depending on the buffer solution used. Isomerization of (IIβ) to (IIα) has been observed, and the factors affecting the rate of isomerization established.

EXPERIMENTAL

HPLC analysis of the reaction mixture was carried out with a Waters chromatograph (USA) with a column (250 × 4.6 mm) packed with the reverse-phase sorbent Silasorb C_{18}, particle

size 6 μliters, with detection by UV at 214 nm. The flow rate of the mobile phase was 1 ml/min, and the column temperature 20°C. The mobile phase consisted of a mixture of phosphate–ammonia buffer (pH 2.0) with methanol in a volume ratio of 6:4. Under the analytical conditions, the retention times of the compounds involved were (min): (I) 11.3, (IIα) 6.2, (IIβ) 5.2, (III) 4.1. The external standard method was used to measure the concentrations of (I), (IIα), (IIβ), and (III). The standards used were the appropriate samples of known concentration (determined by potentiometry). The stabilities of the compounds were examined in 0.5 M $NaHCO_3$ and 0.2 M sodium hydrogen phosphate containing phosphoric acid (pH 7.8), at ambient temperature. The initial concentrations of the compounds in the solutions were around 10 mg/ml (c_0).

LITERATURE CITED

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ANALYSIS OF THE KINETICS OF METHYLURACIL PRODUCTION

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Methyluracil (I) is prepared by condensation of diketene (II) with urea (III) in the presence of acetic anhydride (IV) and pyridine (V). Water is produced by condensation of II with III and, reacting with IV, produces acetic acid (VI) [1].

Analysis of the preparation of I on laboratory [2] and experimental industrial apparatus [6, 7] supported the results of a preliminary qualitative analysis carried out on the supposition [3, 5] that the displacement apparatus used for this strongly exothermic process was close to optimal.

In order to construct a more precise mathematical model of the production of I, and to improve the optimization and efficiency of control systems, a clear analysis of the kinetic mechanism of the various chemical steps of the process is required. This mechanism, considering the formation of the final and side products of the synthesis of I, consists of the following steps:

- the condensation of II and III to form I;
- the degradation of II to form liquid and gaseous product VII;
- the hydrolysis of IV to form VI;
- the acetylation of III by IV, with the formation of acetylurea (VIII);
- the crystallization and precipitation of I_{cr}.

These steps can be shown in a diagram (Fig. 1), which serves as the basis for the analysis of the process.

The preparation of I was studied experimentally with a computerized mathematical model, though the crystallization step was excluded because precipitation does not occur in the continuous reactor.

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