THE BIOLOGICAL ACTIVITY OF PANTOLACTONE AND PANTOIC ACID

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As far as we are aware, no distinction has been made between the biological activity of pantolactone (α,γ-dihydroxy-β,β-dimethylbutyrolactone) and pantoic acid or its ion.¹

In connection with studies on the antagonistic action of pantoyltaurine on salicylate inhibition of Escherichia coli ² we have observed that pantoic acid, or, more properly, the pantoate ion, is more active than pantolactone.

In low concentrations, salicylic acid is thought to inhibit growth of bacteria which synthesize pantothenate (e.g., Escherichia coli) by preventing the formation of pantoic acid or pantolactone (2). If such bacteria are supplied with pantothenic acid, pantoate, or pantolactone, the inhibitory effect of salicylate is nullified. Presumably, the pantoate or pantolactone is used to synthesize pantothenic acid. The fact that pantoate is more active than pantolactone in antagonizing salicylate indicates that pantoate is more readily utilized than pantolactone for the synthesis of pantothenic acid. This suggests that the immediate precursor in the biological synthesis of pantothenic acid is pantoic acid or pantoate rather than pantolactone.

EXPERIMENTAL

A solution of 0.832 per cent (6.4 × 10⁻² M) d(-)-pantolactone³ in 0.1 N sodium hydroxide was hydrolyzed to the pantoate by allowing it to stand at room temperature (29°). The reaction was followed polarimetrically until no further change in rotation was observed. This occurred within an hour. The specific rotation, [α]₂₀ = +13°, compared favorably with that calculated from the data of Frost (3), and indicated

¹ After the completion of this manuscript, the article by Sarett and Cheldelin (1) appeared, in which these authors note that pantoic acid is 4 to 5 times more active than pantolactone as a growth factor for Acetobacter suboxydans. It seems possible that the conditions which they used to hydrolyze the optically active lactone may have racemized the resulting acid. In this case, the relative activity would be twice that given, or about 9 times, as reported for Escherichia coli in the present communication.

² Stansly, P. G., and Alverson, C. M., Science, in press.

³ Specific rotation [α]₀ = -49° (2 per cent solution). We wish to thank the Lederle Laboratories, Inc., for the pantolactone used in this study.

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that hydrolysis was apparently complete. The solution was then diluted with phosphate buffer, pH 6.8, and adjustment of the final solution to pH 6.8 was made with small amounts of dilute hydrochloric acid. The final buffer concentration was 0.02 M with respect to phosphate. This solution was assayed for activity simultaneously with a freshly prepared solution of $8 \times 10^{-3}$ M $d$(-)-pantolactone in 0.02 M phosphate buffer, pH 6.8, after sterilizing by filtration through a sintered glass filter.

The assay consisted of measuring the growth response to various concentrations of pantoate and pantolactone of *Escherichia coli* inhibited by salicylic acid. MacLeod's chemically defined medium (4) containing 28 mg. per cent of salicylic acid was used for these experiments. An inoculum of approximately 6 million viable washed cells per ml. (from a 16 hour broth culture) was used and growth at 37° followed turbidimetrically (5).

Fig. 1 shows the relation between the log of the concentration and the turbidity at 8 hours when multiplication was logarithmic. For any given turbidity, the antilog of the log of the concentration of pantolactone minus the log of the concentration of pantoate expresses the relative activity of the two drugs. The results indicate that pantoate is about 9' times more active than pantolactone in antagonizing salicylate inhibition.
It should be noted that this ratio is merely an expression of the relative activity of two solutions prepared in the described manner. It is possible that at least part of the activity in the solution of pantolactone may actually have been due to pantoate. Frost (3) has shown that a rather slow hydrolysis of pantolactone occurs at pH 6.6 and 60°. However, we have not observed any definite increase in biological activity of a solution of pantolactone allowed to incubate at pH 6.8 for 24 hours at 37°. On the other hand, after 24 hours at 37°, a solution of pantolactone at pH 7.8 was found to be 2.5 times as active as it was initially, indicating hydrolysis of about 28 per cent. The hydrolysis was accompanied by a change in the buffer (0.02 M phosphate) from pH 7.8 to 7.4.

**SUMMARY**

Pantoic acid, or, more properly, the pantoate ion, has been shown to be approximately 9 times more active than pantolactone in antagonizing the inhibitory action of salicylic acid on *Escherichia coli*. This suggests that pantoate is more readily utilized than pantolactone by *Escherichia coli* for the synthesis of pantothenic acid. It therefore appears likely that the immediate precursor in the biological synthesis of pantothenic acid is pantoic acid or pantoate, rather than pantolactone.

**BIBLIOGRAPHY**

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