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Altenin. III. The Synthesis of Altenin

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Ethyl 5-hydroxy-5-(1-hydroxyethyl)-4-oxotetrahydrofuroate was synthesized and was identified with altenin.

The metabolite of fungus *Alternaria Kikuchiana* Tanaka, which causes the black spot disease in the pear, has been isolated and designated "Altenin."¹⁻³ The structure of altenin has been deduced by us to be ethyl 5-hydroxy-5-(1-hydroxyethyl)-4-oxotetrahydrofuroate (I). It has also been pointed out that I is preferred to its tautomers (II, III, IV) in the solution.⁴ This paper will be concerned with the synthesis of altenin.

Results and Discussion

2,4-dioxopentane (V) was chlorinated with sulfuryl chloride to 3-chloro-2,4-dioxopentane (VI),⁵ which in turn gave 3-acetoxy-2,4-dioxopentane (VII) upon treatment with potassium

acetate in acetic acid.⁶ VII was condensed with ethyl glyoxylate in liquid ammonia with two moles of potassium amide passing through the dianion (VIII) of VII.⁷ The condensed product was then treated with ammonium chloride. Under these conditions, although the dianion (VIII) might give the α -ketoaldehyde (IX) by reaction with the ethoxycarbonyl group,⁸ only the expected α -hydroxy ester (X) was separated as a pale yellow liquid, bp 42—47°C/20 mmHg. The infrared absorption spectrum showed the carbonyl absorption band at 1720 cm⁻¹ and the hydroxy band at 3400 cm⁻¹. The ferric chloride reaction showed the characteristic red color of β -dicarbonyl compounds. Therefore, the product was confirmed to be the expected compound, ethyl 5-acetoxy-2-hydroxy-4,6-dioxoheptanoate (X).

As has already been reported,³ altenin is unstable at temperatures above 60°C and loses its phytopathogenic activity. Therefore, the removal

1) I. Hiroe, S. Nishimura and W. Sato, *Tottori Nogei Kagaku Kaishi (Transactions of the Tottori Society of Agriculture Science)*, **11**, 291 (1958).

2) N. Sugiyama, C. Kashima, M. Yamamoto and R. Mohri, *This Bulletin*, **38**, 2028 (1965).

3) N. Sugiyama, C. Kashima, M. Yamamoto, T. Sugaya and R. Mohri, *ibid.*, **39**, 1573 (1966).

4) N. Sugiyama, C. Kashima, Y. Hosoi, T. Ikeda and R. Mohri, *ibid.*, **39**, 2470 (1966).

5) A. Combes, *Compt. Rend.*, **111**, 273 (1890).

6) A. Combes, *ibid.*, **111**, 421 (1890).

7) R. J. Light and C. R. Hauser, *J. Org. Chem.*, **26**, 1716 (1961).

8) S. D. Work and C. R. Hauser, *ibid.*, **28**, 725 (1963).

of protecting acetyl group of X must be accomplished at low temperature. In addition, the ethoxycarbonyl group must not be hydrolyzed to carboxylic acid during this procedure. It was found that the hydrolysis of acetyl group in X and its isomerization to I can be accomplished by treating X with hydrochloric acid in ethanol at 45°C^{9,10}). The reaction product was purified on a silica gel column with a benzene-acetone mixture to give faint yellow liquid. This substance showed infrared absorptions at 3440 and 1060 cm⁻¹ of the hydroxyl group and at 1740 and 1200 cm⁻¹ of the ethoxycarbonyl group. However, the characteristic absorption band of the carboxyl group was not found in the regions from 2800 to 3400 and from 1600 to 1700 cm⁻¹. These spectral data were coincident with those of altenin.⁴⁾ Much like altenin, this substance reduced Tillman's reagent, manganese dioxide, and silver nitrate. All of these data and the results of the elementary analysis support the idea that the structure of this substance is ethyl 5-hydroxy-5-(1-hydroxyethyl)-4-oxotetrahydrofuroate (I).

Furthermore, the R_f value of I on silica-gel thin-layer chromatography with a benzene-acetone mixture, was 0.81, while that of altenin was 0.80. On paper chromatography with water saturated with benzene, the R_f value of I was 0.87, while that of altenin was 0.87. This substance was phytopathogenic to the pear, even when the concentration was 3×10^{-5} mg/ml. Altenin showed a phytopathogenic activity at a concentration of 2×10^{-5} mg/ml. Thus, altenin was synthesized.

It was proved that reductones such as 3-hydroxy-2,4-dioxopentane, which has a partial structure similar to that of altenin, also exhibited the phytopathogenic activity. The details of the biological studies of altenin and related compounds will be reported in another paper.

Experimental

Ethyl 5-Acetoxy-2-hydroxy-4,6-dioxoheptanoate (X). To 250 ml of liquid ammonia in a 500 ml three-

necked flask, a catalytic amount of ferric chloride and 7.8 g of potassium were added in small portions in the course of an hour. This liquid ammonia solution was then kept at -78°C, after which to it there was added 17 g of 3-acetoxy-2,4-dioxopentane (VII) dissolved in 30 ml of anhydrous ether. After one more hour, 9 g of ethyl glyoxylate in 40 ml of anhydrous ether was added, and the mixture was stirred for 5.5 hr. To the dark brown mixture a 25-g portion of ammonium chloride was added, and the ammonia was removed by distillation. The reaction product was then dissolved in water. The aqueous solution was washed with ether and then acidified with hydrochloric acid at about 15°C. The acidic solution was extracted with six to seven 30 ml portions of ether. The combined ether solution was then dried over anhydrous sodium sulfate. After the ether had been removed, the residue was distilled under reduced pressure, bp 42–47°C/20 mmHg; yield, 2 g.

Found: C, 51.77; H, 6.61%. Calcd for C₁₁H₁₆O₇: C, 50.77; H, 6.20%.

Ethyl 5-Hydroxy-5-(1-hydroxyethyl)-4-oxotetrahydrofuroate (I). One gram of X was dissolved in 30 ml of ethanol, and then 1 ml of hydrochloric acid was added. The mixture was stirred for 9 hr at 45°C under a nitrogen atmosphere. After the ethanol had been removed under reduced pressure, the residue was passed through silica-gel (Merck 7729) column with a benzene-acetone (4 : 1 v/v) mixture. A yellow liquid which showed positive Tillman and manganese dioxide tests was thus obtained (yield, 200 mg).

Found: C, 49.60; H, 6.94%. Calcd for C₉H₁₄O₆: C, 49.54; H, 6.47.

The R_f value on silica-gel (Wakogel B-5) thin-layer chromatography with a benzene-acetone (1 : 1 v/v) mixture was 0.81, while that of altenin was 0.80. The R_f value on paper (Toyo paper No. 53) chromatography with water saturated with benzene at 18°C was 0.87, while that of altenin was 0.87.

The Phytopathogenic Activity of I. A solution of synthesized I in an ammonium acetate buffer (pH 7.6) was tested on plucked leaves of the pear (*Pyrus ussuriensis* var. *Aromatic* Rehder). A solution with the concentration of 3×10^{-5} mg/ml produced black spots. This value is nearly the same as that of altenin (2×10^{-5} mg/ml).

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9) H. Böhme and H. Schneider, *Chem. Ber.*, **91**, 1100 (1958).

10) G. Hesse and H. Stahl, *ibid.*, **89**, 2414 (1956).