QUINOLINE DERIVATIVES AS DEGRADATION PRODUCTS FROM ANTIBIOTIC THIOPEPTIN B

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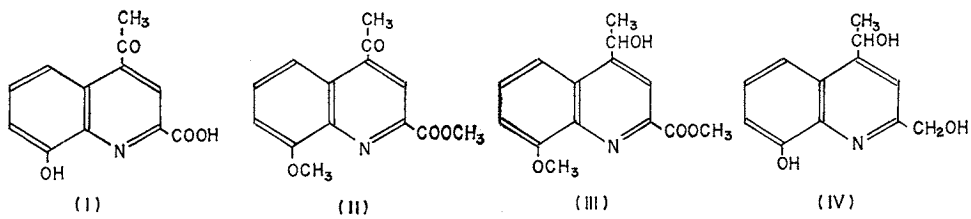
The thiopeptins are sulfur-containing peptide antibiotics produced by *Streptomyces tateyamensis*[1]. They differ from other members of this antibiotic group such as thiostrepton[2] and the siomycins[3] in their sulfur content, amino acid constitutions, chromatographic behavior, and so on. In this paper, we wish to report the isolation and identification of quinaldic acid derivatives from the hydrolysate of thiopeptin B, the major component of the thiopeptins, and also of 2-hydroxymethylquinoline derivative from the hydrolysate of $NaBH_4$-reduced thiopeptin B.

Thiopeptin B (0.95 g) was hydrolyzed with 6 N hydrochloric acid for 24 hours at 100°C. After removal of hydrochloric acid, the residue was dissolved in water. The solution was extracted with ether, and the ether layer was evaporated. When the ethanol solution of the remaining yellow-brown powder (182 mg) was allowed to stand in a refrigerator, yellow needles (7 mg) crystallized. The structure of this substance was confirmed to be 4-acetyl-8-hydroxyquinaldic acid[4,5] (I) on the basis of the IR, NMR, and mass spectra. M.p. 235~240°C; UV, λ_{max}^{MeOH} 262 mμ ($E_{1cm}^{1\%}$ 1760), 375 mμ ($E_{1cm}^{1\%}$ 118). Anal. Calcd. for $C_{12}H_9NO_4$: C 62.34, H 3.92, N 6.06; Found: C 62.33, H 3.93, N 6.13.

The mother liquid of I was treated with diazomethane and the resulting methyl esters were purified on a silicagel column with chloroform. The first ester isolated was methyl 4-acetyl-8-methoxy-quinaldate (II)[4] (yellow needles, 15.6 mg), the structure of which was ascertained in the same way as described for I. M.p. 157~162°C; UV, λ_{max}^{MeOH} 262 mμ ($E_{1cm}^{1\%}$ 860), 362 mμ ($E_{1cm}^{1\%}$ 80). Anal. Calcd. for $C_{14}H_{13}NO_4$: C 64.86, H 5.05, N 5.40; Found: C 65.15, H 4.93, N 5.45. The second ester isolated from the column chromatography, also in the form of yellow needles (40 mg), was shown to be methyl 4-(1'-hydroxyethyl)-8-methoxyquinolidate (III)[4,5]. M. p. 170 ~ 175°C; UV, λ_{max}^{MeOH} 255 mμ ($E_{1cm}^{1\%}$ 1880), 307 mμ ($E_{1cm}^{1\%}$ 148), 345 mμ ($E_{1cm}^{1\%}$ 144). Anal. Calcd. for $C_{14}H_{15}NO_4$: C 64.36, H 5.79, N 5.36; Found: C 64.59, H 5.66, N 5.42.

In the structural investigation of thiostrepton[6], evidence for the presence of an ester linkage between a quinaldic acid precursor and the rest of the molecule was found when the 2-hydroxymethylquinoline derivative (IV) was isolated after hydrolyzing the thiostrepton reduced with $NaBH_4$. A carbonyl band at 1750 cm^{-1} in the IR spectrum of thiostrepton also supports the presence of this ester bond. In the IR spectrum of thiopeptin B, too, a carbonyl band at 1735 cm^{-1} was also observed. Thus, the presence of an ester bond in this antibiotic was assumed and therefore it was treated in a way similar to thiostrepton. Thiopeptin B (3.00 g) was reduced with $NaBH_4$ (1.50 g) and hydrolyzed in 6 N hydrochloric acid. After evaporating the solution, the residue was dissolved in water. The



(I) (II) (III) (IV)

solution was treated with ethylacetate in a separately funnel and then neutralized with sodium bicarbonate. The quinoline compound was extracted with ether and ethylacetate from the aqueous solution and was obtained as crystalline hydrochloride (80 mg) after evaporation of the solvent followed by recrystallization of the residue (207 mg) from ethanol - HCl - acetone. It was further purified by recrystallization from ethanol - acetone. M.p. 186~190°C; UV, $\lambda_{max}^{H_2O}$ 245 mμ (ε 39,300). Anal. Calcd. for $C_{12}H_{13}NO_3 \cdot HCl$: C 56.37, H 5.52, N 5.48, Cl 13.9; Found: C 56.02, H 5.50, N 5.47, Cl 14.04. The NMR spectrum of this compound agreed with that of 2-hydroxymethyl-4-(1'-hydroxyethyl)-8-hydroxyquinoline (**IV**).

These results show that the carboxyl group of the precursor of quinaldic acid in thiopeptin B binds with the hydroxy group of the rest of the molecule through ester linkage in the same way as in thiostrepton. The optical rotation of the hydrochloride of **IV** isolated from thiopeptin B, $[\alpha]_D^{31}$ −87° (*c* 0.29, ethanol), was also almost the same as that from thiostrepton. This means that the configuration of the substituents on the α-carbon of the hydroxyethyl group at position 4 of the quinoline ring is the same in both antibiotics. According to the results of crystallography on thiostrepton by ANDERSON *et al.*[7], this configuration is sinister.

The crystallographic analysis of thiostrepton[7] revealed that the six-carbon ring of quinoline derivatives isolated from the hydrolysate of the antibiotic is produced by aromatization of the substituted cyclohexadiene ring of the precursor in the intact molecule during hydrolysis with acid. In thiopeptin B, the same reaction is assumed because no absorption band was observed above 320 mμ, and also, the extinction coefficients in this region were very small in comparison with those of quinaldic acid derivatives.

Accordingly, it is concluded that thiopeptin B resembles thiostrepton and the siomycins in terms of the formation of quinaldic acid derivatives during degradation and also in high sulfur content. Further investigation of the chemical structure of thiopeptin B is in progress.

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