SYNTHESES OF ALTHIOMYCIN AND ITS ANALOGS IN RELATION TO THEIR ANTIBACTERIAL ACTIVITIES

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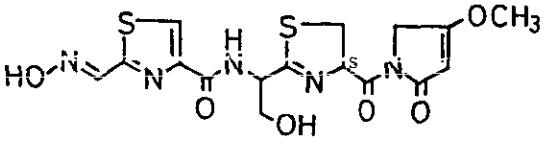
Althiomycin is an antibiotic found by H. Umezawa and his collabolators in 1957 from *Streptomyces althioticus*. It manifests a very wide antibacterial spectrum not only for Gram-positive but also Gram-negative microorganisms. In spite of such remarkable biological activities, it has not been in practical use because of instability of the activity and insolubility in water. In order to modify properties of this antibiotic for the purpose of reuse, we investigate the synthetic chemistry of althiomycin.



althiomycin

First, we aimed a total synthesis of the unique structure of the antibiotic. The synthetic principle is based on the coupling of the thiazoline moiety with the pyrrolinone part followed by linking the thiazole moiety. Two novel methods were actually introduced in this synthesis: (1) new coupling techniques of the thiazolinecarboxylic acid with imino group in the pyrrolinone ring either by a photochemical reaction with diketene or through a reaction of the active ester of cysteine with sodium salt of pyrrolinone. (2) hydroxymethylation at exo methylene linked with C_2 in thiazoline ring by use of aldol condensation.

Thus we could achieve the total syntheses of althiomycin of natural form as well as epi-althiomycin which has an epimeric configuration at C_4 in thiazoline ring.

Furthermore, the thiazoline-pyrrolinone moiety lacking the thiazole part in althiomycin was prepared. The fact that this fragment of the natural compound did not exhibit any antibacterial activity, indicates clearly an importance of the presence of the thiazole moiety in the molecule. We are now engaging in preparations of other fragments or analogs such as thiazole-thiazoline fragment, dehydroxymethyl althiomycin, thiazole-thiazole-pyrrolinone analog and so on in order to discuss much on relationship between structure and activity of this antibiotic.