CHEMISTRY OF β-LACTAM ANTIBIOTICS. A NOVEL SYNTHESIS OF 7α-METHOXY AND OTHER 7α-SUBSTITUTED CEPHALOSPORINS

Hiroaki Yanagisawa, Masami Fukushima, Akiko Ando, and Hideo Nakao

Central Research Laboratories, Sankyo Co.,
Shinagawa, Tokyo 140

A new facile synthesis of 7α-methoxycephalosporins (I) which show strong antimicrobial activity and other 7α-substituted cephalosporins (II) is reported. The Schiff base (III) prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and diphenylmethyl 7-aminocephalosporanate (IV) was oxidized with lead dioxide in benzene to afford the corresponding quinoidal compound (V). Addition of methanol into a solution of V in benzene or $C_2H_4Cl_2$ gave diphenylmethyl 7β-(3,5-di-tert-butyl-4-hydroxybenzylidenamino)-7-methoxycephalosporanate (VI) which was treated with Girard T reagent (VII) in methanol to give 7α-methoxy derivative of IV (VIII: about 70% yield from IV). Acylation of VIII with phenylacetyl chloride in a presence of N,N-diethylaniline and cleavage of diphenylmethyl group by CF_3COOH afforded I which was identical with the authentic sample in physical constants and antimicrobial activity. The other oxidation method of III to VI was studied. Addition of the base ($LiOCH_3$, DBU or Triton B) into a solution of III in THF-methanol at -50° gave the phenolate anion which was then treated with the halogenating agent (tert-BuOCl, NBS, NBA, NCA or Br_2) to afford VI in a similar yield to PbO_2 oxidation. Addition of EtOH, n-PrOH, $NCCH_2OH$, $MeOCH_2CH_2OH$, MeSH, HCN, $CH_2(COOEt)_2$ and HN_3 into V gave the corresponding 7α-substituted Schiff base (IX). Treatment of IX from HN_3 with VII in methanol gave VIII. Hydrolysis of the other IX with VII and acylation with thienylacetyl chloride followed by removal of diphenylmethyl group by CF_3COOH afforded the corresponding II.