

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

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A new facile synthesis of 7 α -methoxycephalosporins (I) which show strong antimicrobial activity and other 7 α -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 7 β -(3,5-di-tert-butyl-4-hydroxybenzylidenamino)-7-methoxycephalosporanate (VI) which was treated with Girard T reagent (VII) in methanol to give 7 α -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 7 α -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.