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A NOVEL GENERAL METHOD FOR SYNTHESIZING 7α-METHOXYCEPHALOSPORINS

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Since the suggestion by Strominger and Tipper[1] that 6-methyl penicillins and 7-methyl cephalosporins should have enhanced antimicrobial activity, a number of 6 or 7-substituted penicillins or cephalosporins have been synthesized. Particularly the recent discoveries of Cephamycin C series and the derived 7α-methoxycephalosporins[2] which have especially strong and unique antimicrobial activity[3] accelerate enormous efforts to introduce 7α-methoxy group to cephalosporin nucleus. The methods reported to date are as follows: nucleophilic attack of methanol on 7-azido-7-bromocephalosporins in the presence of $AgBF_4$,[4] methanol addition to 7-acylaminocephalosporins[5] and conversion of 7-methylthio[6] or 7-halocephalosporins[7] to the corresponding 7-methoxy derivatives.

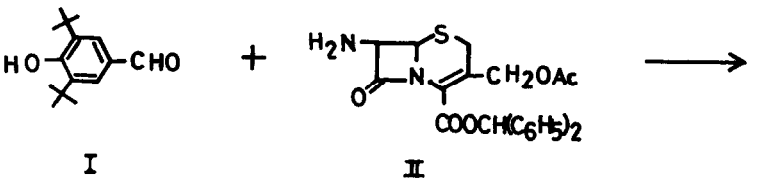
We now wish to report a novel and attractive method for 7β-amino-7α-methoxycephalosporanate which is the most important key intermediate for synthesizing all kinds of derivatives of 7α-methoxycephalosporins. This method which involves the original oxidation of Schiff base followed by addition of methanol is superior to the abovementioned ones in the easiness of the practical procedure and yield.

A typical procedure is as follows. The Schiff base (III) prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde (I) and diphenylmethyl 7-aminocephalosporanate (II) in the usual manner was oxidized with freshly prepared lead dioxide in benzene at room temperature for 1 hr yielding the corresponding quinoidal compound (IV): ir ($CHCl_3$) 1770, 1740, 1610 cm^{-1} (no OH absorption

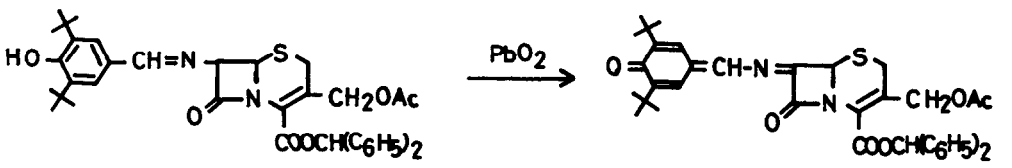
stretching); nmr ($CDCl_3$) δ 1.33 (s, tert-Bu), 2.00 (s, OAc), 3.45, 3.65 (ABq, J=19, C-2 H), 4.77, 5.05 (ABq, J=13, C-3 methylene), 5.37 (s, C-6 H), 7.00 (s, $C\underline{H}(C_6H_5)_2$), 7.33 (s, $CH(C_6\underline{H}_5)_2$), 7.69 (d, J=3, CH=N), 7.87 (d, J=3, ). After removal of lead oxide, IV was <u>in situ</u> treated with excess methanol at room temperature for several hours. Evaporation of solvents gave the 7α-methoxy derivative (V) as yellowish powder: ir ($CHCl_3$) 3630, 1770, 1740, 1630 cm^{-1}; uv (EtOH) 291 nm; nmr ($CDCl_3$) δ 1.45 (s, tert-Bu), 1.98 (s, OAc), 3.18, 3.47 (ABq, J=18, C-2 H), 3.55 (s, OCH_3), 4.62, 4.93 (ABq, J=13, C-3 methylene), 5.03 (s, C-6 H), 5.50 (s, OH), 6.97 (s, $C\underline{H}(C_6H_5)_2$), 7.30 (s, $CH(C_6\underline{H}_5)_2$), 7.63 (s, benzylidene Ph), 8.45 (s, CH=N).

Treatment of V with Girard T reagent in methanol at room temperature for 30 min gave the free amine (VI).[4,5c] The overall yield of VI from II was 70%. Acylation of VI with phenylacetyl chloride and N,N-diethylaniline in dichloroethane at 0°, followed by removal of the diphenylmethyl protecting group with trifluoroacetic acid in anisole at 0° gave the required 7α-methoxy-cephalosporin (VII)[8]: mp 162°; ir (KBr) 3300, 1780, 1730, 1700, 1660 cm^{-1}; uv (EtOH) 247, 268 nm; nmr (DMSO-d_6) δ 1.98 (s, OAc), 3.20, 3.57 (ABq, J=17, C-2 H), 3.29 (s, OCH_3), 3.52 (s, $C_6H_5C\underline{H}_2CONH$), 4.58, 4.89 (ABq, J=13, C=3 methylene), 5.00 (s, C-6 H), 7.12 (s, C_6H_5).

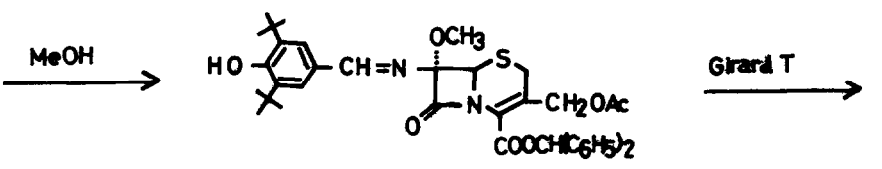
The α configuration of the 7-methoxy group of VII was supported by the agreement of the nmr spectrum and the antimicrobial activity with that of an authentic sample prepared by known methods.[5,8] The stereospecific formation of V from IV can be accounted for by methanol addition from the less hindered α-side.



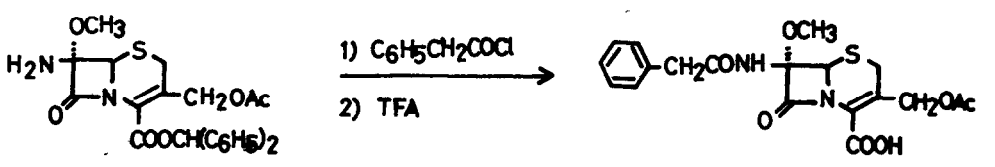
I II



III IV



V



VI VII

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