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THE SYNTHESIS OF 7α-METHOXY-7β-AMIDOCEPHALOSPORANIC ACIDS BY METHOXYLATION OF 7β-(p-NITROBENZYLOXYCARBOXAMIDO) CEPHALOSPORANIC ACID

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The cleavage procedures of Sletzinger (1) and Lunn (2) provide routes for obtaining new 7α-methoxycephalosporins from the naturally occurring 7α-methoxy-7β-aminoadipamido compounds (3). However, the ready availability of parent unmethoxylated β-lactam antibiotics has resulted in considerable recent synthetic effort to substitute the 7α-methoxy group on the β-lactam ring.

A Merck group has reported (4) an approach involving diazotization of 7β-aminocephalosporins and 6β-aminopenicillins, and subsequent treatment of the diazo compounds with haloazides then methanol; while Baldwin and coworkers (5) utilized t-butyl hypochlorite followed by methanol in a procedure for the introduction of the methoxyl group into the β-lactam ring of penicillin sulfoxides. Various groups have also employed the solvolysis of halo and methylthio Schiff bases with some success (6a-d).

The most straightforward techniques to date are those of Christensen (7a) and Koppel (7b). These involved the low temperature formation of the anions of 7β-amidocephalosporins and 6β-amidopenicillins, oxidation of these by t-butyl-hypochlorite, base elimination to acylimines and alcohol addition, all in the one reaction vessel, to give the required alkoxy compounds. However, in several instances these procedures led to complications. Thus, for example, low yields were obtained when the acyl side residue itself formed an anion.

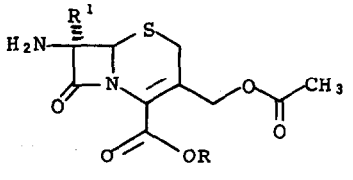
Extension of this technique to cephalosporins and penicillins with a removable amine protecting group would provide a facile synthesis of 7α-methoxy amino nuclei, which could be acylated at will. We describe below the achievement of this goal by oxidation of the anion of p-nitrobenzylcarbamates.

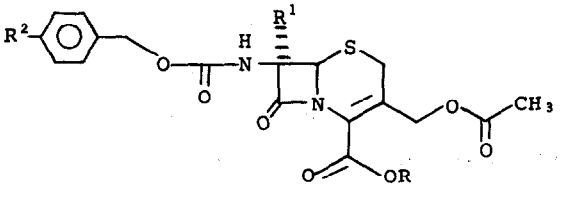
The conversion of 7β-aminocephalosporanic acid (7-ACA) (1) to benzhydryl 7β-(p-nitrobenzylcarbamoyl)cephalosporanate (3) was accomplished by treatment of 7-ACA, in acetonitrile, with bis-(trimethylsilyl)acetamide then p-nitrobenzylchloroformate, and esterifying the resulting carbamoyl acid 2 with diphenyldiazomethane in tetrahydrofuran.

The methoxylation of 3 to 4 was carried out by the method of Koppel. Trimethylphosphite was added prior to allowing the reaction mixture to warm up, this being found to prevent any overoxidation by the excess t-butyl hypochlorite. When the methoxy compound 4 was hydrogenated in methanol-THF, using 5% palladium-on-charcoal as catalyst, exactly 3 moles of hydrogen were taken up and an unstable product, probably 5, was obtained.

Pure 7α-methoxy-7β-aminocephalosporanic acid benzhydryl ester (6) was obtained by stirring the crude hydrogenation product 5 for 2 hr with an equal weight of Merck Silica Gel (<200 mesh) in methylene chloride, filtering and removing solvent under reduced pressure to give a solid foam, nmr ($CDCl_3$): δ H-6 4.85 (s), OCH_3 3.49 (s). The overall yield of 6 from 7-ACA was 68%.

Acylation of 6 using acid chlorides and pyridine in cold chloroform or methylene chloride, followed by removal of the benzhydryl protecting group with trifluoracetic acid provided the required 7α-methoxycephalosporins. The nmr signals for the C-6 proton of the amides thus produced are clean singlets in the range δ 5.17-5.05, characteristic of 7α-methoxy-β-amidocephalosporanic acids (2).





1 R = R^1 = H

6 R = $(C_6H_5)_2CH$; R^1 = OCH_3

2 R = H; R^1 = H; R^2 = NO_2

3 R = $(C_6H_5)_2CH$; R^1 = H; R^2 = NO_2

4 R = $(C_6H_5)_2CH$; R^1 = OCH_3; R^2 = NO_2

5 R = $(C_6H_5)_2CH$; R^1 = OCH_3; R^2 = NH_2

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