Tetrahedron Letters No. 14, pp 1307 - 1310, 1974. Pergamon Press. Printed in Great Britain.

CLEAVAGE OF 7α-METHOXYCEPHALOSPORIN C DERIVATIVES WITH PHOSPHORUS PENTACHLORIDE

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(Received in USA 24 December 1973; received in UK for publication 21 February 1974)

Reports of naturally occurring 7α-methoxycephalosporin compounds (1) and a procedure for converting them to other 7α-methoxy-7β-amidocephalosporanic acids (2) have recently appeared in the literature.

There are many instances of phosphorus pentachloride being used to convert 7β-amidocephalosporins and 6β-amidopenicillins to their imidoyl chlorides, and then cleaving these to the corresponding amines (3). In some unpublished work at these laboratories this sequence was applied to 7α-methoxycephalosporins and, while paper chromatography indicated cleavage, the low yields made isolation of products extremely difficult.

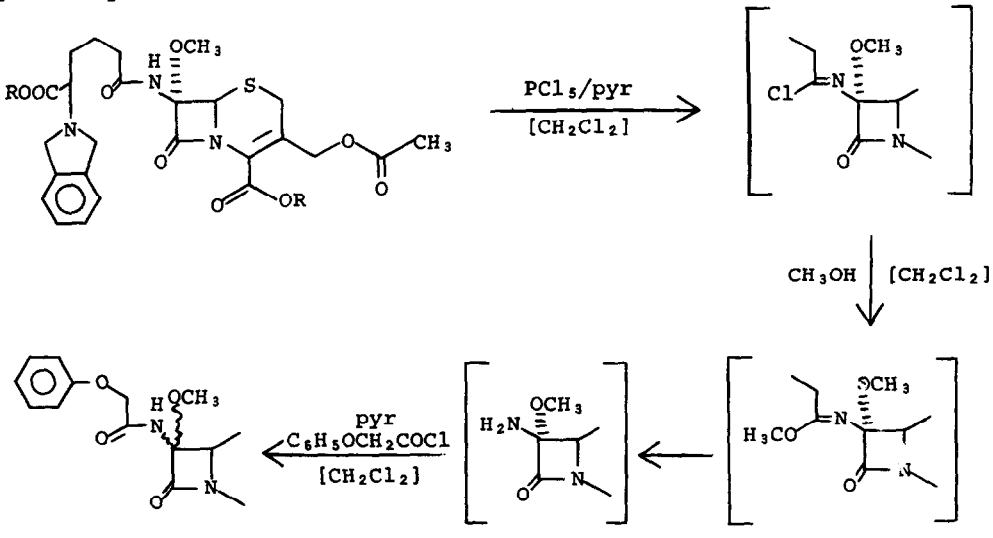
We outline below studies of the phosphorus pentachloride cleavage which have led to a ready procedure for replacing the aminoadipoyl side chain of 7α-methoxycephalosporin C derivatives with other acyl functions. Appropriate conditions were determined by carrying out the reactions in nmr tubes and following their course by nmr spectroscopy.

Using N-phthaloyl cephalosporin C esters as models, we found we could follow imidoyl chloride formation (occurring on treatment with phosphorus pentachloride and pyridine in methylene chloride) by observing the characteristic downfield shift of the signal for the methylene group, $-\underline{CH_2}CONH-$, of the adipoyl side chain. This signal appears as part of a broad 4-proton resonance centered at about δ 2.35 in the amides and as a 2-proton triplet, at δ 2.74 ($\underline{J}\sim 7$ cps), in the imidoyl chloride spectra.

Whereas with N-phthaloylcephalosporin C diesters this change is complete within 30 min at 0°, an hour at 25° is required for the corresponding 7α-methoxy compounds.

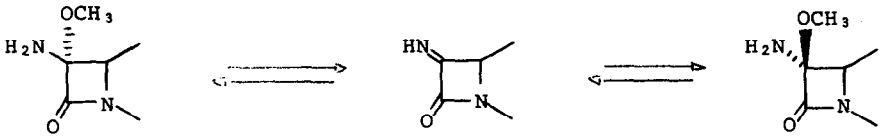
Treatment of the N-phthaloylcephalosporin C diester imidoyl chlorides with methanol at 0° resulted in the disappearance of the above-mentioned triplet, the signal for the two protons again becoming part of a broad one centered at about δ 2.35 (4 protons). Then addition of D_2O, shaking, and phase separation resulted in the appearance of 7β-aminocephalosporanic acid ester (presumably as the hydrochloride salt) in the aqueous phase, the side chain residue remaining in the organic phase.

Similar processing with the 7β-methoxy compounds produced very little 7-amino nucleus in the aqueous phase. However, if pyridine and phenoxyacetyl chloride were added with cooling after completion of the methanolysis of the imidoyl chlorides, and prior to the addition of water, then 40% yields of epimeric mixtures of 7-methoxy-7-phenoxyacetamidocephalosporins were readily isolated. The nmr spectra of the two epimers are very similar, a prime difference being the chemical shifts for the C(6)H protons. This signal lies in the range δ 5.17-5.05 with naturally occurring 7β-aminoadipoylaminocephalosporins and this range is maintained in a series of 7α-methoxycephalosporins prepared by independent syntheses in these laboratories. In the 7β-methoxy compounds this signal is at slightly lower field (around δ 5.22). The ratio of 7α- to 7β-methoxy epimers was about 1:6 and 1:2 for diethyl and dibenzhydryl esters, respectively.



Until now it has been assumed (4) that alcohols convert imidoyl chlorides to imidoyl ethers which are then hydrolyzed to amines by the addition of water. However, our own results with the methoxy compounds are consistent with other findings in these laboratories (5): that alcohols, themselves, convert cephalosporin imidoyl chlorides to amines, water being unnecessary. On the other hand, our studies indicate that under mildly acidic anhydrous conditions a relatively stable species, probably the imidoyl ether, is formed. The signal for the presumed $-\underline{CH_2}-C(OCH_3)=N$ protons appeared at δ 2.60.

Concerning the mechanism of epimer formation, it is instructive that when d_4-methanol was used to methanolyze the 7α-methoxy-7β-imidoyl chloride, the isolated phenoxyacetamido epimers were found to be 7-OCD_3 compounds. The nmr spectrum exhibits a parent ion with mass 453.1277 (theory for $C_{20}D_3H_{19}N_2O_6S$, 453.1285) as opposed to 450.1106 for the 7-OCH_3 compounds (theory 450.1097). We suggest that following methoxyamine formation an equilibrium is established:



ACKNOWLEDGEMENT

We wish to thank Dr. L. D. Hatfield for his ready suggestions and advice.

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