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A NEW METHOD FOR CLEAVAGE OF 7-AMIDE GROUP OF CEPHALOSPORINS

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Naturally occurring cephalosporin C and cephamycin C,[1] which have an aminoadipoyl side chain at the C-7 position, are starting materials for many modified analogues exhibiting more broad antibiotic activity against many bacteria. To cleave aminoadipoyl side chain of cephalosporin C to 7-aminocephalosporanic acid, there is an excellent method which utilizes phosphorous pentachloride[2], and also Merck groups reported two procedures to exchange that of cephamycin C for thiopheneacetyl group.[3] In this paper, we wish to report another new route to cleave 7-amide group of cephalosporin derivatives. This procedure may have potential for applying to both cephalosporin C and cephamycin C.

It is known that the reaction of N-monosubstituted amides (1, R^1=H, Cl, C_6H_5, etc.) with oxalyl chloride produces 2-methyleneoxazolidine-4,5-dione derivatives (3)[4] via the intermediate (2). If 2 could be stabilized without activation of the methylene hydrogens adjacent to R^1 by electron-withdrawal or conjugative effect leading to 3, it might persist in the reaction mixture and would react with water (alcohol) to cleave to a carboxylic acid (ester) and an oxamic acid (ester). We first chose α-pyrrolidone (4a, n=3) and α-piperidone (4b, n=4) to examine this inference.

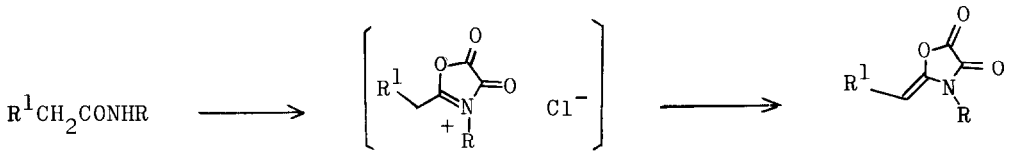
The reaction of 4a with 1.5 eq. oxalyl chloride in benzene at 5° for 30 min gave an unstable salt (5a, n=3) as white crystals[5] which was treated with methanol at 0-10° for 1-5 hr to yield oxamic acid methyl ester (6a, n=3): oil; MS m/e 203 (M^+); uv λ_{max}(EtOH) 223.5 nm (ε=4280). And the same treatment of 4b afforded 5b (n=4) which was further converted to 6b (n=4): oil; MS m/e 217 (M^+); uv λ_{max}(EtOH) 223 nm (ε=4310). Thus, it was proved that our assumption was correct. We applied these results to formation of 7-carboxycarbonylaminocephalosporin derivatives. Successive treatment of methyl (6R,7R)-7-n-butylamido-3-methyl-3-cephem-4-carboxylate (7a, X=H) with 1.5-2.0 eq. of oxalyl chloride in benzene at 20° for 3-4 hr, and with water-acetone or aq. sodium bicarbonate or phosphate buffer at 5-10° for 1-24 hr, produced methyl (6R,7R)-7-carboxycarbonylamino-3-methyl-3-cephem-4-carboxylate (8a, X=R=H) in 70-80% yield: mp 186-187°; MS m/e 300 (M^+); ir ν_{max}(nujol) 3270, 1775, 1728, 1688, 1679, 1640 cm^{-1}; nmr δ (DMF-d_7) 1.98 (3H, s, C_3-CH_3), 3.42 (2H, s, SCH_2), 3.64 (3H, s, $COOCH_3$), 5.06 (1H, d, J=5 Hz, C_6-H), 5.59 (1H, d,d, J=5, 10 Hz, C_7-H), 9.18 (1H, d, J=10 Hz, NH), 10.68 (1H, bs, COOH). Analogously, 7a was treated with oxalyl chloride, followed by the reaction with methanol at 20°

for 20 hr to afford 8b (X=H, R=CH_3) in 80% yield: mp 130-131.5°. Reaction of methyl (6R,7S)-7-n-butylamido-7-methoxy-3-methyl-3-cephem-4-carboxylate (7b, X=OCH_3) with 1.5 eq. each of oxalyl chloride and powdered sodium carbonate in dry dioxane at 5° for 12 hr, and with water, gave an oily mixture, which was separated by column chromatography on silica gel (15% water impregnated) to produce methyl (6R,7S)-7-carboxycarbonylamino-7-methoxy-3-methyl-3-cephem-4-carboxylate (8c, X=OCH_3, R=H)[6] in 67% yield: powder; MS m/e 330 (M^+); ir ν_{max}(KBr) 3400 (broad), 1775, 1720, 1630 cm^{-1}; nmr δ (DMF-d_7) 2.16 (3H, s, C_3-C$\underline{H}_3$), 3.46 (2H, s, SC$\underline{H}_2$), 3.59 (3H, s, OC$\underline{H}_3$), 3.85 (3H, s, COOC$\underline{H}_3$), 5.18 (1H, s, C_6-$\underline{H}$), 7.16 (1H, s, N$\underline{H}$), 9.47 (1H, s, COO$\underline{H}$). Neither double bond isomerization nor epimerization at chiral centers occurred under these conditions. This procedure was equally applicable to the formation of penicillin oxamic acid derivatives.

These oxamic acids (8a and 8c) have a high potential for leading to the corresponding free amines and acyl exchanged amides under mild conditions without cleavage of β-lactam ring. Actually we could develop a new method for this transformation by use of carbodiimides under neutral condition. This procedure was equally useful for the convertion of penicillin 6-oxamic acid derivatives to amines.

The reaction of 8a in dry dioxane or methylene chloride with 1.1 eq. of diphenylcarbodiimide[7] at 25° for 1 hr gave methyl (6R,7R)-7-amino-3-methyl-3-cephem-4-carboxylate (10a) in 72% yield which was identical with an authentic sample[8] in all respects. Treatment of 8a with 1.2 eq. of dicyclohexylcarbodiimide (DCC) in methylene chloride at 25° for 30 min afforded an unstable 1:1 adduct (9) in 75% yield which gradually changed to 10a and a stable rearranged product (11) on standing at room temperature. The physical data of 11 are shown: foam; ir ν_{max}(nujol) 3320, 3250, 1780, 1728, 1695, 1685, 1665, 1628 cm^{-1}; nmr δ ($CDCl_3$) 0.6-2.3 (20H, m), 2.13 (3H, s, C_3-C$\underline{H}_3$), 3.35 (2H, bs, SC$\underline{H}_2$), 3.97 (3H, s, COOC$\underline{H}_3$), 3.4-4.2 (2H, m, 2x>C<(H/N)), 4.94 (1H, d, J=5 Hz, C_6-$\underline{H}$), 5.68 (1H, dd, J=5, 9 Hz, C_7-$\underline{H}$), 6.25 (1H, d, J=8 Hz, cyclohexyl-N$\underline{H}$CO), 8.43 (1H, d, J=9 Hz, CON$\underline{H}$-C_7). On the other hand, treatment of 8a with 2.5 eq. of DCC in methylene chloride at 25° for 1 hr, and subsequent silica gel chromatography yielded three products: 11 (24%), 12a (21%); foam; MS m/e 488 (M^+); nmr δ ($CDCl_3$) 4.92 (1H, d, J=2 Hz, C_6-$\underline{H}$), 5.03 (1H, d, J=2 Hz, C_7-$\underline{H}$), and 12b (13%); foam; nmr δ ($CDCl_3$) 5.15 (1H, d, J=4.5 Hz, C_6-$\underline{H}$), 5.67 (1H, d, J=4.5 Hz, C_7-$\underline{H}$). And also 8c reacts with DCC to afford the imidazolidinone (12c, 36%); mp 163-164°; MS m/e 518 (M^+) uv λ_{max}(EtOH) 267.6 nm (ε=16000); ir ν_{max}(nujol) 1773, 1725, 1700 cm^{-1}; nmr δ ($CDCl_3$) 1.0-2.2 (20H, m), 2.10 (3H, s, C_3-C$\underline{H}_3$), 3.1-4.2 (2H, m, 2x>C<(H/N)), 3.15, 3.50 (2H, AB-q, J=18 Hz, SC$\underline{H}_2$), 3.66 (3H, s, OC$\underline{H}_3$), 3.90 (3H, s, COOC$\underline{H}_3$), 4.99 (1H, s, C_6-$\underline{H}$), and amidine (13, 6%); mp 179-181°; MS m/e 437 (M^+). The structure of 12c was further confirmed by hydrolysis of the C=N bond with 1 eq. of p-toluenesulfonic acid monohydrate in acetone at 25° for 16 hr to afford dicyclohexylimidazolidintrione[9]; mp 175°, and methyl (6R)-7-oxo-3-methyl-3-cephem-4-carboxylate.[10]

The reaction of 8c with 1.1 eq. of diphenylcarbodiimide in methylene chloride at 0° for 1 hr as mentioned above (in the case of 8a) produced (7S)-7-methoxy-7-



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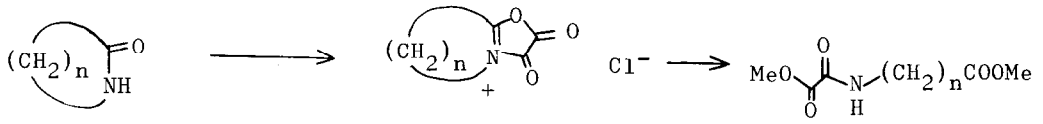
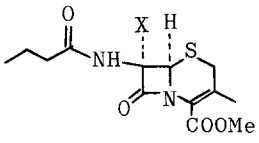
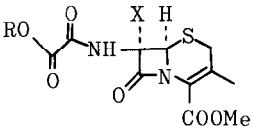


4 a, n=3
b, n=4

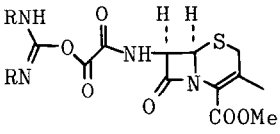
5 6



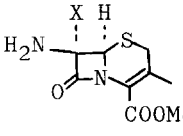
7 a, X=H
b, X=OMe



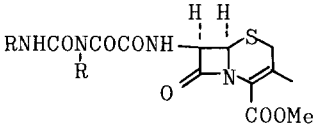
8 a, X=R=H
b, X=H, R=Me
c, X=OMe, R=H



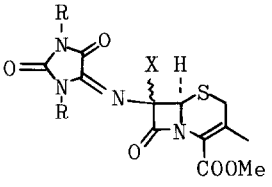
9 R=cyclohexyl



10 a, X=H
b, X=OMe

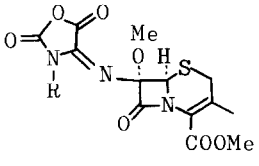


11 R=cyclohexyl

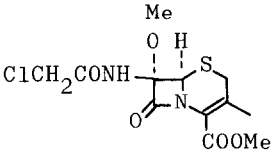


R=cyclohexyl

12 a, X= —H
b, X= ---H
c, X= ---OMe



13 R=cyclohexyl



14

amino derivative (10b) which was further reacted with monochloroacetyl chloride and N,N-dimethylaniline at 25° for 16 hr to give methyl (6R,7S)-7-methoxy-7-chloroacetamido-3-methyl-3-cephem-4-carboxylate (14) in 40% yield; foam; MS m/e 334(M^+); ir ν_{max}(nujol) 3260, 1785, 1725, 1680 cm^{-1}; nmr δ ($CDCl_3$) 2.20 (3H, s, C_3-CH_3), 3.30 (2H, s, SCH_2), 3.60 (3H, s, OCH_3), 3.88 (3H, s, $COOCH_3$), 4.20 (2H, s, $ClCH_2CO$), 5.12 (1H, s, C_6-H), 7.95 (1H, s, CONH). Neither double bond isomerization nor epimerization at chiral centers occurred under these conditions.

Thus diphenylcarbodiimide was found to be a convenient reagent for the conversion of N-monosubstituted oxamic acids to N-monosubstituted free amines under mild conditions.

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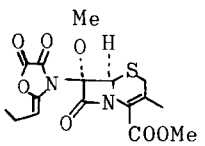
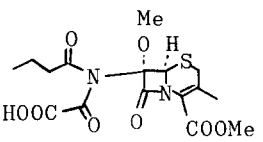
5. The salts (5a) and (5b) were unstable at room temperature. They gradually changed to methyleneoxazolidine-4,5-dione derivatives by loss of hydrogen chloride.
6. On treatment of 7b with oxalyl chloride in benzene at 20° for 2 hr without powdered sodium carbonate, there were obtained 8c' (28%), mp 157-158°, and 8c" (3%) as minor products in addition to 8c as major product.



8c'



8c"

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8. The authentic sample (10a) was prepared from methyl (6R,7R)-3-methyl-7-phenylacetamido-3-cephem-4-carboxylate by phosphorous pentachloride method.
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