

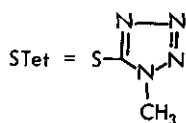
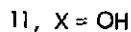
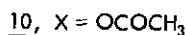
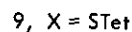
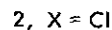
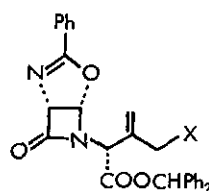
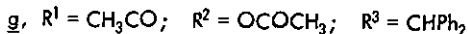
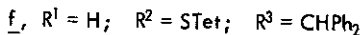
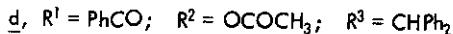
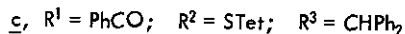
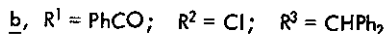
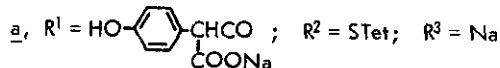
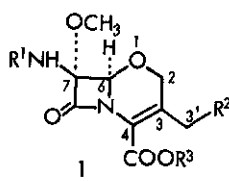
CONVENIENT SYNTHESIS OF 3'-SUBSTITUTED METHYL 7 α -METHOXY-1-OXACEPHEMS¹

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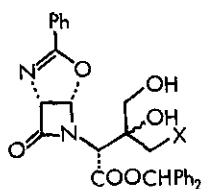
Abstract — A convenient synthesis of the title compounds 1 is achieved by formation of glycols 3, 12, 13 and 14 or chlorohydrins 6 from epioxazolines having pertinent allylic substituents, followed by stereoselective, intramolecular etherification to 4, 7, 15, 16 and 17, elimination to 5, 18 and 19, and further conversions.

Since 7 α -methoxy-1-oxacephem 1a was found to possess remarkable antibacterial activity,² persistent efforts in our laboratories have been directed towards efficient and industrially feasible synthesis of 3'-substituted methyl derivatives such as 1b and 1c.²⁻⁶ Functionalization at C-3' of 3-methyl 1-oxacepems has not been fruitful^{7,8} in contrast to successful allylic bromination at C-3' of the 1-thia congeners.⁹ Conversion of epioxazolinoazetidinone allylic chloride 2 into 3-chloromethyl-1-oxacephem 5 is an essential part in our previous promising



synthesis,⁵ but it consists of five steps involving an industrially unfavorable photochlorination. We now report a convenient, three-step process for conversion of 2 into 5 utilizing glycol or chlorohydrin formation and application of this process to synthesis of 3'-substituted methyl 7 α -methoxy-1-oxacephems.

According to a procedure reported from our laboratories for synthesis of 3-methyl 1-oxacephems,⁷ allylic chloride 2⁵ was oxidized (KClO₃/catalytic OsO₄, THF-H₂O, 25 °C) to glycols 3 as an isomeric mixture, which, without separation, underwent stereospecific, intramolecular etherification (catalytic CF₃CO₂H, CH₂Cl₂, 25 °C) to give a mixture of 3-chloromethyl-3-hydroxy-1-oxacephams 4¹⁰ in 72% overall yield. Repeated chromatography¹⁰ of the mixture afforded 3 α -hydroxy isomer 4a^{11,12} and 3 β -isomer 4b^{11,13} in 19 and 32% yields, which were dehydrated (SOCl₂/ α -picoline, CH₂Cl₂, 0 °C) to the same Δ^3 -product 5^{5,10} in 40 and 63% yields, respectively. This dehydration result contrasts with our earlier observation⁵ that the reaction of 3 β -hydroxy-3-methyl analog (X = H in 4b) gave a Δ^2 -product as a major product. When the above three-step conversion was carried out without separation of the isomers, the product 5¹⁰ was obtained in 40% overall yield from the allylic chloride 2. In an alternative, new approach, 2 was treated with trichloroisocyanuric acid in aq acetone at 20 °C to give an isomeric mixture of chlorohydrins 6,¹⁴ which were cyclized (catalytic BF₃·Et₂O, AcOEt, 20 °C) to an inseparable mixture of 3-chloro-3-chloromethyl compounds 7.¹⁴ Dehydrochlorination (1,5-diazabicyclo[5.4.0]-undec-5-ene, CH₂Cl₂, -20 °C) of the mixture afforded the 1-oxa-3-cephem 5¹⁰ in 32% overall yield

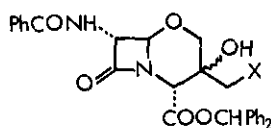


3, X = Cl

12, X = STet

13, X = OCOCH₃

14, X = OH

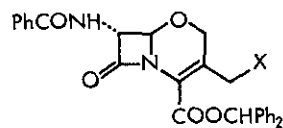


4a; 4b, X = Cl

15a; 15b, X = STet

16a; 16b, X = OCOCH₃

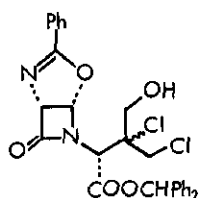
17a; 17b, X = OH



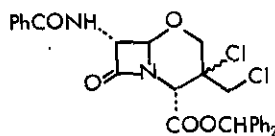
5, X = Cl

18, X = STet

19, X = OCOCH₃



6a; 6b



7a; 7b

from 2 with no appreciable amount of its Δ^2 -isomer being isolated.

The glycol process was extended to synthesis of 3-(1-methyl-1H-tetrazol-5-ylthio)methyl and 3-acetoxymethyl derivatives 18 and 19. Since the allylic chloride 2 is not reactive enough for nucleophilic substitution without double bond migration, the starting olefins 9 and 10 were prepared by treatment of more reactive allylic iodide 8⁵ with sodium 1-methyl-1H-tetrazole-5-thiolate (TetSNa) ($\text{Me}_2\text{CO-MeOH}$, 20 °C) and with AgBF_4 in DMA at 20 °C in 92 and 82% yields, respectively. An alternative preparation of the allylic acetate 10 (43% yield) without using the expensive silver reagent is acetylation (AcCl/PhNEt_2 , CH_2Cl_2 , 20 °C) of allylic alcohol 11,⁵ which itself serves as a starting material for synthesis of the 3-acetoxymethyl compound 19 via diols 17. Oxidation of olefins 9, 10, and 11 as described above gave glycols 12 and 13 as isomeric mixtures and triol 14 as a crystalline single isomer (mp 134-136 °C), which on intramolecular etherification (catalytic $\text{BF}_3 \cdot \text{Et}_2\text{O}$, AcOEt , 20 °C) were converted into epimeric mixtures of 3-hydroxy derivatives 15, 16, and 17,¹⁵ respectively. The 3-hydroxymethyl derivatives 17 were quantitatively acetylated ($\text{Ac}_2\text{O/pyridine}$, 0 °C) to 16. Dehydration ($\text{SOCl}_2/\text{pyridine}$, CH_2Cl_2 , 25 °C) of 15 and 16 gave 1-oxa-3-cephem derivatives 18^{10,16} and 19^{10,17} in overall yields of 22% from 9 and 32% from 10 (35% from 11 via 17), respectively.

The above synthesis of the 3-acetoxymethyl-1-oxacephem 19 is significant, since substitution of the 3-chloromethyl derivative 5 did not proceed smoothly under usual conditions (NaOAc/DMF , AgOAc/HOAc etc.) in contrast to facile conversion of 5 into 18 (TetSNa/catalytic Bu_4NBr , $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$, 25 °C; 80% yield).

The acetate 19 underwent 7 α -methoxylation (t-BuOCl-LiOMe , CH_2Cl_2 , -40 °C) to 1d^{10,18} (81% yield) followed by the side-chain cleavage ($\text{PCl}_5/\text{pyridine}$, CH_2Cl_2 , 25 °C; MeOH , 0 °C; Et_2NH , -8 °C) to give methoxy amine 1e,¹⁹ the nucleus for preparation of various 3-acetoxymethyl-7 α -methoxy-1-oxacephem antibiotics.²⁰ On the other hand, the 7 α -methoxylation of the tetrazolylthiomethyl derivative 18 was difficult owing to its low solubility in an applicable solvent such as CH_2Cl_2 . Conversion of the 3-chloromethyl compound 5 into 1f and further into the antibiotic 1a has been reported.^{5,2}

In conclusion, the present approach provides an alternative, convenient synthesis of the antibiotic 1a in the shortest steps and of 3-acetoxymethyl-7 α -methoxy-1-oxacephems. Successful application to synthesis of other 3'-substituted methyl derivatives will be highly feasible.

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10. The product(s) was separated or purified by chromatography (silica gel, C_6H_6 -AcOEt) and/or crystallization.
11. The α or β configuration of the 3-substituent was determined by 1H - and ^{13}C -NMR studies which will be published in a separate paper.
12. 4a, 11 3 α -hydroxy isomer: foams; ir (CHCl₃) 3550 (br), 3440-3200, 1782, 1745, 1670 cm^{-1} .
13. 4b, 11 3 β -hydroxy isomer: mp 132-134 °C (ether-acetone); $[\alpha]_D^{25} +48.8 \pm 0.9^\circ$ (c 1.020, CHCl₃); ir (CHCl₃) 3550 (br), 3450-3200, 1780, 1740, 1665 cm^{-1} .
14. Chromatographic separation¹⁰ gave 6a and 6b, the latter being partly changed into the corresponding lactone. The acid-catalyzed cyclization of the isomers afforded the epimeric dichloride 7a and 7b. 7a, 11 3 α -chloroisomer: mp 190-191 °C (decomp) (ether); $[\alpha]_D^{25} +15.6 \pm 1^\circ$ (c 0.537, CHCl₃); ir (CHCl₃) 3444, 1787, 1749, 1680 cm^{-1} . 7b, 11 3 β -chloro isomer: foams; ir (CHCl₃) 3430, 3325, 1785, 1740, 1675 cm^{-1} .
15. The α and β epimers were separated¹⁰ and characterized¹¹ except for 15a and 15b whose NMR spectra were too complicated for interpretation. 15a: foams; ir (CHCl₃) 3435, 3300 (br), 1780, 1745, 1675 cm^{-1} . 15b: foams; ir (CHCl₃) 3525, 3410, 1780, 1743, 1679 cm^{-1} . 16a, 11 3 α -hydroxy isomer: foams; ir (CHCl₃) 3580, 3440, 1785, 1752, 1675 cm^{-1} . 16b, 11 3 β -hydroxy isomer: mp 142-143 °C (CH₂Cl₂-ether); $[\alpha]_D^{25.5} +29.2 \pm 1.3$ (c 0.501, acetone); ir (CHCl₃) 3560 (br), 3430 (br), 1784, 1750, 1710 (sh), 1675 cm^{-1} . 17a, 3 α -hydroxy isomer: foams; ir (CHCl₃) 3450 (br), 1790-1760, 1665 cm^{-1} ; nmr (CDCl₃) δ 3.4-4.3 (m, 6, C₂ H, C₃ H, OH), 4.86 (br s, 1, C₄ H), 4.96 (d, 1, J = 8 Hz, C₇ H), 5.36 (br s, 1, C₆ H), 6.90 (s, 1,

- CHPh₂), 7.1-7.9 (m, 16H, ArH and NH). 17b, 3 β -hydroxy isomer: foams; ir (CHCl₃) 3425 (br), 1790, 1745 (sh), 1715, 1675 cm⁻¹; nmr (CDCl₃) δ 3.26 (br s, 3, C₃, H, OH), 3.75 (br s, 2, C₂ H), 4.71 (s, 1, C₄ H), 5.08 (d, 1, J = 7 Hz, C₇ H), 5.46 (s, 1, C₆ H), 6.90 (s, 1, CHPh₂), 7.2-7.9 (m, 16, ArH and NH).
16. 18: mp 203-205 °C; [α]_D²² -116.1 $\pm$ 3.2° (c 0.492, dioxane); ir (CHCl₃) 3450, 1792, 1725, 1680 cm⁻¹; nmr (CDCl₃) δ 3.77 (s, 3, NCH₃), 4.20 (s, 2, C₃, H), 4.57 (s, 2, C₂ H), 4.90 (d, 1, J = 7 Hz, C₇ H), 5.07 (s, 1, C₆ H), 6.93 (s, 1, CHPh₂), 7.2-7.9 (m, 16, ArH and NH).
17. 19: foams; ir (CHCl₃) 3380 (br), 1785, 1735 (br), 1665 cm⁻¹; nmr (CDCl₃) δ 2.00 (s, 3, COCH₃), 4.41 (s, 2, C₂ H), 4.92 (s, 3, C₃, H, C₆ H), 5.06 (d, 1, J = 8 Hz, C₇ H), 6.88 (s, 1, CHPh₂), 7.15-7.90 (m, 16, ArH and NH).
18. 1d: foams; ir (CHCl₃) 3425, 1785, 1740, 1685 cm⁻¹; nmr (CDCl₃) δ 1.96 (s, 3, COCH₃), 3.56 (s, 3, OCH₃), 4.41 (s, 2, C₂ H), 5.00 (s, 2, C₃, H), 5.15 (s, 1, C₆ H), 6.90 (s, 1, CHPh₂), 7.00 (s, 1, NH), 7.2-7.5 and 7.7-7.9 (m, 15, ArH).
19. This amine is somewhat unstable and usually used for acylation without purification. For example, treatment with AcCl-py at 0 °C afforded acetylamino derivative 1g (45%). 1g: nmr (CDCl₃) δ 2.00 (s, 6, OCOCH₃, NHCOCCH₃), 3.55 (s, 3, OCH₃), 4.48 (s, 2, C₂ H), 5.03 (br s, 2, C₃, H), 5.06 (s, 1, C₆ H), 6.40 (br s, 1, NH), 6.91 (s, 1, CHPh₂), 7.2-7.6 (m, 10H, ArH).
20. Synthesis and biological activity of the antibiotics will be published in separate papers.

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