SYNTHESIS OF 3-(1-METHYL-1,2,3,4-TETRAZOL-5-YL AND 2-METHYL-1,3,4-THIADIAZOL-5-YL-OXYMETHYL)-3-CEPHEM DERIVATIVES[1]

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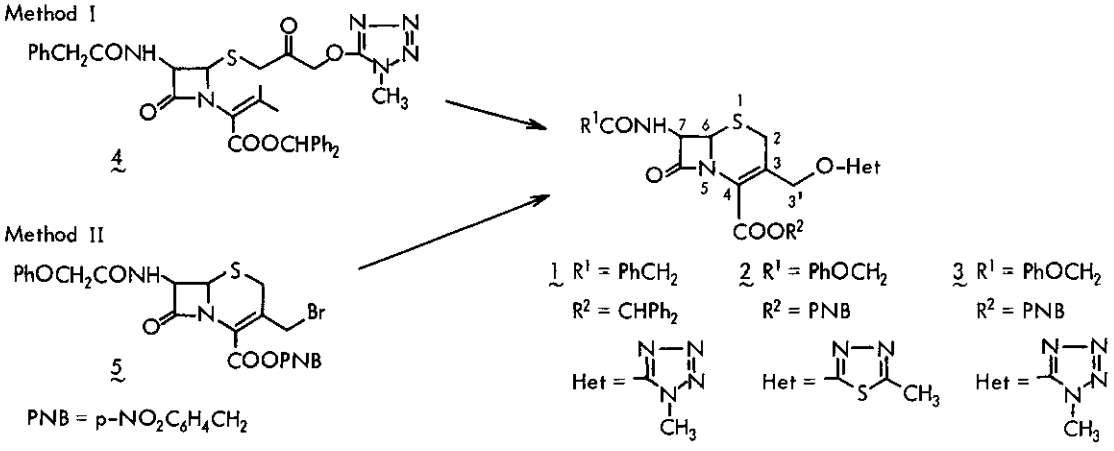
Abstract — Cephem derivatives possessing a heterocyclic oxymethyl group at position 3 were synthesized by two methods as the benzhydryl 1 or p-nitrobenzyl esters 2 and 3. However, removal of the ester protecting groups to obtain the free acids was unsuccessful.

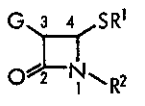
Since Cefazolin was reported to have extensive antibacterial activity,[2] a number of analogous cephalosporin derivatives possessing a heterocyclic thiomethyl group at position 3 have been synthesized and examined for clinical use.[3] To our best knowledge, however, no one has yet reported synthesis of the corresponding heterocyclic oxymethyl derivatives which may be interesting because the electronegative oxygen may enhance the antibacterial activity. We wish to report the synthesis of the title compounds 1, 2 and 3 by the two synthetic methods shown in the following scheme.



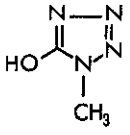
The first method involved compound 4 as a key intermediate, in which a heterocycle and an oxymethyl group were already incorporated. We planned to cyclize 4 to cephem after sequential reaction.[4] In the second approach, the 3-bromomethyl-3-cephem derivative 5[5] was subjected to substitution reaction with a heterocyclic ambident anion to introduce a hetero-oxy group leading to the desired compounds 2 and 3.

1-a) Synthesis of intermediate 4

First, reaction of 4-diazoacetonylthio-azetidinone derivative 6 with 1-methyl-5-hydroxy-1,2,3,4-tetrazole 7[6] seemed suitable for our purpose, because α-diazoketone in the presence of BF_3 reacts with alcohol to form an ether linkage.[7] Penicillin G benzhydrylester was converted into thiazoline-azetidinone 8,[8] which underwent an acid-catalyzed ring opening reaction with 30% perchloric acid in acetone to give the 4-mercaptoazetidinone compound 9.[9] Conversion of 9 into the corresponding silver thiolate 10 followed by a coupling reaction with methyl chloroacetate and successive alkaline hydrolysis afforded a thioglycollic acid derivative 11, which was treated with oxalyl chloride in the presence of a catalytic amount of DMF in benzene and the resulting acid chloride was converted with diazomethane into the α-diazoketone 6 [δ:[10] 2.90 (2H, s, $SC\underline{H}_2CO$), 4.95-5.40 (3H, m, $C\underline{H}N_2$, C_3-H and C_4-H); ν cm^{-1}: 3420, 2110, 1771, 1725, 1683] in 80% yield. The reaction of 6 with tetrazole 7 in the presence of $BF_3 \cdot Et_2O$ in benzene only afforded an oxazoline compound 12.[11] When 6 was subjected to a decomposition reaction with $BF_3 \cdot Et_2O$ in acetic acid, 3,4-trans-acetoxyazetidinone 13 [δ: 2.23 (3H, s, $OCOC\underline{H}_3$), 4.96 (1H, d-d, J 7 and 2 Hz, C_3-H), 5.96 (1H, d, J 7 Hz, C_4-H); ν cm^{-1}: 3420, 1785, 1725, 1686] was obtained, suggesting that decomposition of 6 would follow the formation of a sulfur ylide or a sulfonium ion by intramolecular nucleophilic attack of the sulfur to the carbene center or α-ketodiazonium ion,



6 $R^1 = CH_2COCHN_2$
9 $R^1 = H$
10 $R^1 = Ag$
11 $R^1 = CH_2CO_2H$



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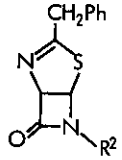

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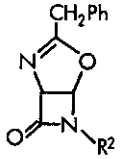

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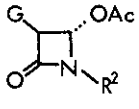

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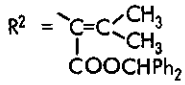
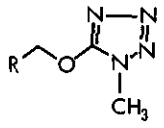
G = $PhCH_2CONH$

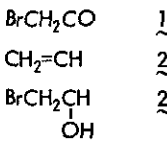
R^2 = 

leading to compound 12 or 13 depending upon the reaction conditions.

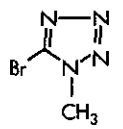
A convergent synthesis of 4 was achieved using a coupling reaction of 1-methyl-1,2,3,4-tetrazol-5-yl-oxymethyl bromomethyl ketone 14 with 10. The bromoketone 14 was prepared as follows. Treatment of 1-methyl-5-bromo-1,2,3,4-tetrazole 15[12] with sodium allylate afforded the allyl ether 16 [δ: 3.80 (3H, s), 5.00 (2H, d, J 6 Hz), 5.32-6.50 (3H, m); ν cm^{-1}: 1580, 1490, 1460, 1422, 1320] in 71% yield, which was converted to the bromohydrin 17 with N-bromoacetamide-p-*TsOH* in aq dioxane in 79% yield. Oxidation of 17 with Jones reagent in acetone gave the bromoketone 14 [δ: 3.93 (3H, s), 4.07 (2H, s), 5.47 (2H, s); ν cm^{-1}: 1745, 1591, 1500, 1309] in an unexpectedly poor yield (13%) along with a large amount of 1-methyltetrazol-5-yl-oxyacetic acid 18. Other milder oxidizing reagents (N-chlorotriazole, NiO_2, dimethyl azodicarboxylate, Oppenauer reagent) were tried



14 R = $BrCH_2CO$
16 R = CH_2=CH
17 R = $BrCH_2CH(OH)$
18 R = CO_2H



19 R = CH_3CO
20 R = CH≡C
21 R = BrC≡C



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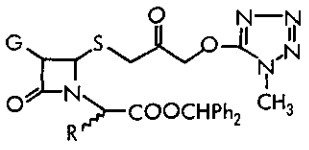
without success. In order to improve the yield of 14, the methyl ketone 19 [m.p. 73°; δ ppm: 2.25 (3H, s), 3.95 (3H, s), 5.18 (2H, s); ν cm^{-1}: 1745, 1580, 1496, 1309, 1055] was prepared in 75% yield by reaction of 15 with sodium propargylate affording propargyl ether 20 [m.p. 54°; δ: 2.68 (1H, t, J 3 Hz), 3.83 (3H, s), 5.15 (2H, d, J 3 Hz); ν cm^{-1}: 3300, 2125, 1580, 1490, 1360, 1300, 1050] followed by hydration of the latter in the usual way (*$HgSO_4$-H_2SO_4-MeOH*). Bromination of 19 with pyridinium hydrobromide perbromide-AcOH, $CuBr_2$-EtOH, or Br_2-AcOH, however, were unsuccessful. On treatment of 20 with sodium hypobromite generated in situ (Br_2-aq NaOH, 0°), the bromoacetylene 21 [m.p. 92°; δ: 3.87 (3H, s), 5.22 (2H, s); ν cm^{-1}: 2225, 1580, 1490, 1360, 1300, 980] was formed in 76% yield, then was hydrated with *HgO-BF_3·Et_2O-CCl_3COOH-MeOH*[13] to afford a slightly improved yield (19%) of 14.

Reaction of 14 with the thiolate 10 proceeded quite smoothly in HMPA at room temperature to afford the intermediate 4 [δ: 3.02 (2H, s, SCH_2CO), 3.80

(3H, s, NCH_3), 4.85, 5.30 (4H, m, $COCH_2O$, C_3-H and C_4-H); ν cm^{-1}: 1772, 1730, 1682, 1580] in 90% yield.

1-b) Conversion of intermediate 4 to the 3-cephem 1

Compound 4 was converted to the 3-cephem compound 1 according to a reaction sequence developed in this laboratory.[4] Ozonolysis of 4 and reduction of the α-ketoester 22 formed in situ with Zn in acetic acid followed by chlorination of the resulting α-hydroxyester 23 with $SOCl_2$-pyridine in CH_2Cl_2 yielded the α-chloroester 24 which was treated with triphenyl phosphine to afford the ylide 25 [ν cm^{-1}: 1768, 1738, 1675, 1730, 1580] in 50% overall yield. The final cyclization was achieved by refluxing a benzene solution of 25 for 20 hr, which yielded the desired compound 1 [δ: 3.55 (2H, broad s, C_2-H), 3.67 (5H, s, N-CH_3 and CH_2Ph), 5.00 (1H, d, J 5 Hz, C_6-H), 5.20, 5.50 (2H, each d, J 13 Hz, C_3'-H), 5.94 (1H, d-d, J 9 and 5 Hz, C_7-H); ν cm^{-1}: 3405, 1795, 1730, 1687, 1572, 1493] in 25.5% yield accompanied by a 30% recovery of 25 after purification by SiO_2 column chromatography.



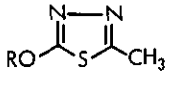
22 R = O(=)
23 R = OH
24 R = Cl
25 R = PPh_3(=)

2) Substitution reaction of 3-bromomethyl-3-cephem 5

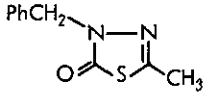
In view of the great difficulty involved in the first method, we turned our attention to the alkylation reaction of the ambident anion derived from heterocyclic alcohol with 3-bromomethylcephem 5 to directly introduce a hetero-oxy group into position 3' of the cephem nucleus. Tieckelmann and his co-workers[14] reported that the reaction site, O vs. N, depends markedly on the kind of metal cation used in the alkylation of pyridone.

As a preliminary experiment, sodium and silver salts of 2-methyl-5-hydroxy-1,3,4-thiadiazole 26[15] were allowed to react with benzyl bromide. The sodium salt of 26 on treatment with benzyl bromide in DMF afforded exclusively the N-alkylation product 27 (ν cm^{-1}: 1675) in 81% yield, while the silver salt favored O-alkylation in benzene to give 28 (79%; ν cm^{-1}: 1487) together with 27 (11%). The silver salt of 7 yielded only the O-alkylation product 29 (ν cm^{-1}: 1575) in 90% yield.

Based on these findings, p-nitrobenzyl, 7-phenoxyacetamido-3-bromomethyl-3-cephem-4-carboxylate 5 was subjected to the displacement reaction with the silver salt of 26 under the O-alkylation conditions affording the titled compound 2 [16.5%; δ: 2.62 (3H, s, CH_3), 3.64 (2H, broad s, C_2-H), 5.24, 5.69 (2H, each d, J 14 Hz, C_3'-H); ν cm^{-1}: 3410, 1793, 1735, 1695, 1490, 1350] and the starting material 5 (30%) without contamination by N-alkylated product. On the other hand, the reaction with the sodium salt of 26 gave rise to formation of the N-alkylated 2-cephem 30 [δ: 2.41 (3H, s, CH_3), 6.46 (1H, s, C_2-H); ν cm^{-1}: 1786, 1756, 1690] in 31% yield with a small amount of 5 (11%).



26 R = H
28 R = CH_2Ph



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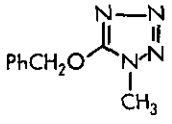

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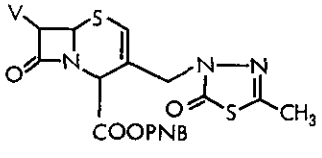

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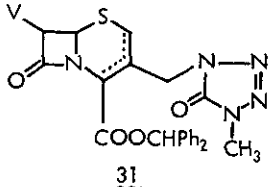

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In the reaction of the silver salt of 7 with 5, only the O-alkylated 3-cephem 3 [16%; δ: 3.64 (2H, broad s, C_2-H), 3.81 (3H, s, NCH_3), 5.31, 5.65 (2H, each d, J 12 Hz, C_3'-H); ν cm^{-1}: 3405, 1795, 1732, 1695, 1600, 1570, 1490, 1350] was obtained with a 10% yield of recovered 5. Sodium salt 7, however, yielded both kinds of product, a predominant yield of N-alkylated 2- and 3-cephem 31 [42% as a 3:2 mixture; δ: 3.62 (3H, s, NCH_3), 3.45 (0.8H, broad s, C_2-H), 6.60 (0.6H, s, C_2-H); ν cm^{-1}: 1787, 1755, 1738, 1725, 1605] and a small amount of 3 (8%).

Unfortunately, various attempts to remove carboxyl protecting groups have been unsuccessful (CF_3COOH-anisole, $AlCl_3$-anisole,[16] medium-pressured hydrogenation) due to the labile nature of the ether linkage binding electron-withdrawing heterocycles to allylic carbon.

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