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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. 19.[1] SYNTHESIS OF 3'-NOR-TYPE 1-OXACEPHEMS

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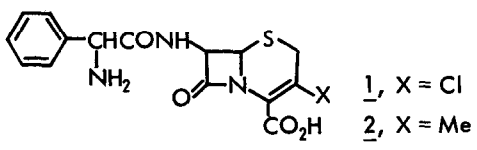
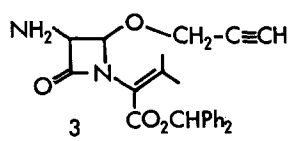
Summary: Synthesis of optically active 3'-nor-type 1-oxacephems from 6-APA was described. p-Nitrobenzyl 7β-amino-3-chloro-7α-methoxy-1-oxa-3-cephem-4-carboxylate 39 was also prepared.

Chauvette et al.[2a] described that some 3-norcephalosporins showed antibacterial activity equivalent to naturally occurring cephalosporins, among which 7-(D-2-amino-2-phenylacetamido)-3-chlor-3-cephem-4-carboxylic acid 1 (Cefaclor)[2b] is found to have an antibacterial activity higher than Cefalexin 2 (X = Me), a widely used oral cephalosporin. It has been known that replacement of the sulfur atom at position 1 of the cephem nucleus with oxygen enhances the biological activity.[3a,b] To date, however, there is no report on synthesis of an optically active 3'-nor-type 1-oxacephem nucleus except an ambiguous synthesis reported in the patent literature.[4] We have succeeded in synthesizing the 3-hydroxy-1-oxacephem nucleus and some 3'-nor-type derivatives. Our synthetic plan is to use the azetidinone propargyl ether 3[5] derived from 6-APA as the starting material and to apply the intramolecular Wittig reaction to an activated carboxylic acid for constructing the desired 3-hydroxy-1-oxacephem nucleus.



1, X = Cl
2, X = Me

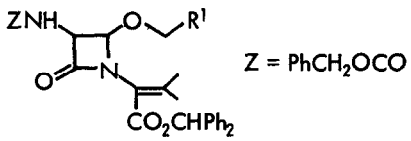


3

Preparation of azetidinone 3 from 6-APA has already been reported from our laboratories.[5] Compound 4[6] prepared from 3 was selectively hydrogenated (Pd-C, $CaCO_3$, MeOH) to allylic ether 5 (98%), which was treated with mCPBA to give epoxide 6 (81.2%). An isomeric mixture of glycols 8 was obtained in 94% yield on treating 6 with $HClO_4$ in aqueous acetone followed by hydrolysis of the partially formed acetonide 7. Oxidative cleavage of 8 with HIO_4 afforded aldehyde 9, which was subsequently submitted to further oxidation (CrO_3, acetone) to the carboxylic acid 10 (92%). The isopropylideneacetate moiety of methyl ester 11[7] obtained from 10 (CH_2N_2, CH_2Cl_2) was converted into the triphenylphosphoranylideneacetate group by the procedure established in our laboratories,[8] involving ozonolysis and successive reduction (O_3, -78°C, CH_2Cl_2; then Zn, HOAc, -50°C to ambient temp) to a 1:1 mixture of epimeric alcohols 12, chlorination of 12 (3 mol equiv $SOCl_2$, pyridine, CH_2Cl_2, 0°C, 30 min) to a mixture of chlorides 13, and treatment with

PPh_3 (CH_2Cl_2, reflux, 2 hr) to afford ylide 14 in 78% overall yield from 11. Alkaline hydrolysis of 14 (1.0 mol equiv NaOH, aqueous acetone, 0°C, 30 min) gave acid 15 quantitatively.

An applicable intramolecular reaction between an activated carboxylic acid and the phosphorous ylide has been briefly reported by Woodward[9] in synthesis of a 3-acetoxycephem derivative. Treatment of 15 with Ac_2O in dioxane gave only degradation products. After an extensive study,[10] the intramolecular Wittig reaction to form the desired 1-oxacephem nucleus was found to proceed smoothly in the presence of dimethylacetamide. Although the role of DMA in this reaction is not clear, it may be reasonably considered to act as a trapping agent of HOAc produced during the reaction and/or a promotor of the mixed anhydride formation. A typical example is given below to illustrate the reaction procedure. To a solution of ylide 15 (7.9 g) in toluene (150 ml) were added DMA (4.44 g) and Ac_2O (20.7 g). After the mixture was heated at 105°C for 16 hr, it was poured into ice-H_2O and extracted with EtOAc. The organic layer was washed with H_2O, saturated aqueous $NaHCO_3$ and H_2O successively, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (C_6H_6:EtOAc:HOAc = 9:1:0.01) to give the desired 3-acetoxy-1-oxacephem ester 17[11] (2.54 g, 48%) and a small amount of 18 (0.81 g, 10.7%) as a by-product. The use of excess DMA in this reaction reduced the yield of 17 and raised the yield of the undesired 18.



Z = $PhCH_2OCO$

4, R^1 = C≡CH

5, R^1 = CH=CH_2

6, R^1 = 

7, R^1 = 

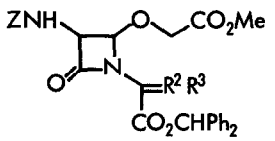
8, R^1 = 

9, R^1 = CHO

10, R^1 = CO_2H

11, R^1 = CO_2Me

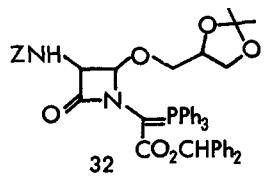
20, R^1 = CO_2Me t-Bu instead of $CHPh_2$



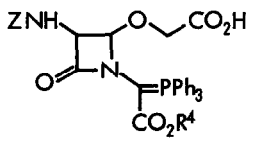
12, R^2R^3 = 

13, R^2R^3 =

14, R^2R^3 = PPh_3



32



15, R^4 = $CHPh_2$

16, R^4 = $CHPh_2$ $PhCH_2CO$ instead of Z

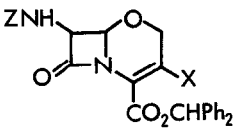
21, R^4 = t-But

24, R^4 = t-But COSPh instead of CO_2H

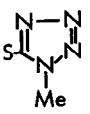
The cyclization reaction is reasonably expected to proceed more efficiently by exchange of the ester moiety for an electron-rich substituent such as t-butoxycarbonyl. Intramolecular cyclization of 21[12] proceeded very smoothly as expected[13] (90°C, 3 hr) to give the desired 3-acetoxy-1-oxacephem 22 (69%), which was smoothly hydrolyzed to 23. Unfortunately, as modification at position 3 did not proceed well on this t-butyl ester 23, although produced in yield better than that of 26, we had to use the latter as the intermediate for preparing 3'-nor-type 1-oxacephems.

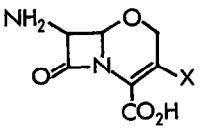
Mild hydrolysis of 17 (aqueous pyridine, room temp, 30 min) quantitatively gave 3-hydroxy-1-oxacephem 26,[14] which was converted into 3-chloro- (mp 130-131°C, 59%) (Ph_3P, Cl_2, CH_2Cl_2, 0°C

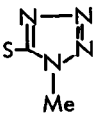
then at room temp, 1.5 hr), 3-methanesulfonyloxy- (mp 67-70°C, 94%) (MsCl, NEt_3, CH_2Cl_2, -50°C, 15 min) and 3-methoxy- (amorph, 75%) (CH_2N_2, CH_2Cl_2, room temp) -1-oxacephems, 27, 28, and 29. Either the chloro or mesyloxy group in 27 or 28 was replaced with the 1-methyltetrazol-5-ylthio group to give 30 (87%) or reductively removed to give 1-oxacephem 31 (95%) (Zn, HOAc-CH_2Cl_2, room temp, 1 hr). Compound 31 was also obtained by an alternative route. Conversion of the acetonide 7 into the phosphorane 32 was achieved similarly. Acid hydrolysis of 32 and successive oxidation (HIO_4) gave the aldehyde, which was treated with $NaHCO_3$ to give the desired 31 though in rather poor yield (6.5% from 7). As selective deblocking of the Z group in these esters was unsuccessful, compounds 27, 28, 29, 30, and 31 were converted respectively into amino acids 33-37 in more than 80% yields by the method[15] ($AlCl_3$, anisole, CH_2Cl_2, room temp, overnight) developed in our laboratories.

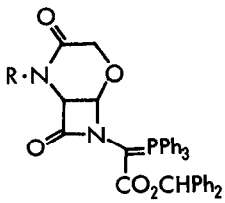


17, X = OCOMe
22, X = OCOMe
t-Bu instead of $CHPh_2$
23, X = OH
t-Bu instead of $CHPh_2$
25, X = SPh
t-Bu instead of $CHPh_2$
26, X = OH

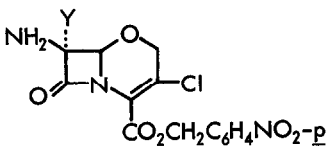
27, X = Cl
28, X = OSO_2Me
29, X = OMe
30, X = 
31, X = H



33, X = Cl
34, X = OSO_2Me
35, X = OMe
36, X = 
37, X = H



18, R = Z
19, R = $PhCH_2CO$



38, Y = H
39, Y = OMe

Next, methoxylation at C_7 of the 7β-amino-3-chlor-1-oxacephem 38 prepared from 27 in four steps[16] was successfully carried out by applying the known method,[17] and the desired 7α-methoxy-1-oxacephem 39[18] was obtained in 35% overall yield.

In conclusion, the present work provides the first synthesis of optically active 3'-nor-type 1-oxacephem nuclei from 6-aminopenicillanic acid. These amino acids described above can be reacylated to give biologically active 3'-nor-type 1-oxacephems, whose antibacterial activity will be reported in a separate paper.

REFERENCES AND NOTES

1. Part 18: M. Kishi, H. Ishitobi, W. Nagata, and T. Tsuji, Submitted for publication in Heterocycles.
2. (a) R. R. Chauvette and P. A. Pennington, J. Amer. Chem. Soc., 96, 4986 (1974); (b) R. R. Chauvette and P. A. Pennington, J. Med. Chem., 18, 403 (1975).
3. (a) R. A. Firestone, J. L. Fahey, N. C. Maciejewicz, G. S. Patel, and B. G. Christensen,

J. Med. Chem., 20, 551 (1977); (b) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, ibid., 22, 757 (1979).

4. S. Wolfe, U. S. Patent No. 4,013,653; claiming priority; British Patent application date, June 30, 1974.

5. M. Narisada, H. Onoue, and W. Nagata, Heterocycles, 7, 839 (1977).

6. 4: foam; δ ($CDCl_3$) 2.00 s 3 H, 2.25 s 3 H, 2.17 d (3 Hz) 1 H, 4.07 d (3 Hz) 2 H, 5.10 d (4 Hz) 1 H, 5.17 s 2 H, 5.33 dd (8, 4 Hz) 1 H, 5.55 d (8 Hz) 1 H, 6.98 s 1 H; ν ($CHCl_3$) 3440, 3300, 1774, 1720, 1630 cm^{-1}.

7. 11: syrup; δ ($CDCl_3$) 2.00 s 3 H, 2.25 s 3 H, 3.58 s 3 H, 3.97 s 2 H, 5.00-5.40 m 2 H, 5.13 s 2 H, 5.57 d (8 Hz) 1 H, 6.93 s 1 H; ν ($CHCl_3$) 3445, 1780, 1725, 1635, 1510 cm^{-1}.

8. S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, Heterocycles, 8, 283 (1977).

9. R. B. Woodward, In "Recent Advances in the Chemistry of β-Lactam Antibiotics", Ed. J. Elks; The Chemical Society, Burington House, London, p 167 (1977).

10. None of the desired 1-oxacephem was obtained in the reaction of 16 with Ac_2O in dioxane, even in the presence of DMA, and unexpected 19 (92%) was isolated.

11. 17: foam; δ ($CDCl_3$) 2.00 s 3 H, 4.32 s 2 H, 5.05 d (4 Hz) 1 H, 5.13 s 2 H, 5.38 dd (10, 4 Hz) 1 H, 5.68 d (10 Hz) 1 H, 6.95 s 1 H; ν ($CHCl_3$) 3445, 1800, 1785, 1725, 1656, 1508 cm^{-1}.

12. Conversion of 20, prepared by the deblocking[15] of the benzhydryl ester ($AlCl_3$, anisole, CH_2Cl_2) and subsequent reesterification (isobutene, H_2SO_4, CH_2Cl_2), into ylide 21 was carried out in a way similar to that used for preparation of 15.

13. As an another example, cyclization of the phenylthio ester 24 prepared from 21 ($(COCl)_2$, pyridine, PhSH, CH_2Cl_2, room temp) proceeded very well giving the corresponding 1-oxacephem 25 (81%, mp 146-148°C) (toluene, reflux, 8 hr).

14. 26: foam; δ ($CDCl_3$) 4.37 s 2 H, 5.05 d (4 Hz) 1 H, 5.18 s 2 H, 5.45 dd (10, 4 Hz) 1 H, 5.72 d (10 Hz) 1 H, 7.00 s 1 H, 10.83 bs 1 H; ν ($CHCl_3$) 3440, 1795, 1725, 1675, 1625, 1510 cm^{-1}.

15. T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, T. Maeda, and W. Nagata, Tetrahedron Letters, 2793 (1979).

16. 1. CF_3CO_2H, anisole, CH_2Cl_2, room temp; 2. NaOAc, EtOAc-MeOH, room temp; 3. p-$O_2NC_6H_4CH_2Br$, DMF, room temp; 4. $AlCl_3$, anisole, CH_2Cl_2, room temp.

17. H. Yanagisawa, M. Fukushima, A. Ando, and H. Nakao, Tetrahedron Letters, 2705 (1975).

18. 39: foam; δ ($CDCl_3$) 1.83 b 2 H, 3.53 s 3 H, 4.54 s 2 H, 5.01 s 1 H, 5.47 s 2 H, (7.67, 8.28) ABq (9 Hz) 4 H; ν ($CHCl_3$) 1790, 1740, 1520, 1350 cm^{-1}.

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