Communications to the Editor

[Chem. Pharm. Bull. 30(8)3061—3064(1982)]

SYNTHESIS OF N^7-HYDROXY- AND N^7-METHOXYCEPHALOSPORINS

Daijiro Hagiwara, Kozo Sawada, Tetsuo Ohnami, and Masashi Hashimoto*

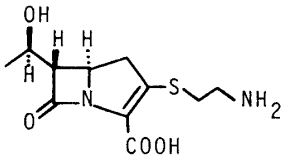
Central Research Laboratories, Fujisawa Pharmaceutical Co., Ltd.
2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

N^7-Hydroxy- (11a,b) and N^7-methoxycephalosporins (13a,b) were synthesized from 7-oxocephems (4a,b) *via* a sequence of reactions involving, as the main steps, oximation [4a,b → 5a,b; 7a,b] and borane reduction [5a,b →6a,b; 7a,b → 8a,b].

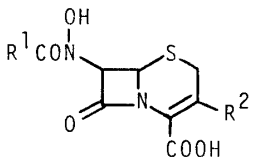
KEYWORDS — cephalosporins; 7-oxocephems; thienamycin; oximation; borane reduction; antibacterial activity

The recent discovery of potent thienamycin-type carbapenem antibiotics (e.g. 1)[1] has stimulated considerable interest in preparing penam and cephem derivatives possessing the hydroxyalkyl moiety at C-6(7),[2] because this side-chain of the carbapenems can be considered to function in the direct binding of the antibiotics to the receptor sites of the bacterial cell-wall enzymes.[3] However, the 6(7)-hydroxyalkyl penam and cephem hybrids so prepared were markedly less active than the parent penicillins and cephalosporins, or almost completely devoid of activity.[2a] This appears to us to be due to the stabilization of their β-lactam rings by the introduction of the electron-donating hydroxyalkyl group α to the β-lactam carbonyl of the penam and cephem nuclei.

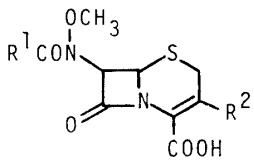
We were therefore interested in preparing the $N^{6(7)}$-hydroxy derivatives of penicillins and cephalosporins (e.g. 2). The presence of such an electron-withdrawing hydroxyamide moiety at C-6(7) might contrariwise increase the chemical



1



2



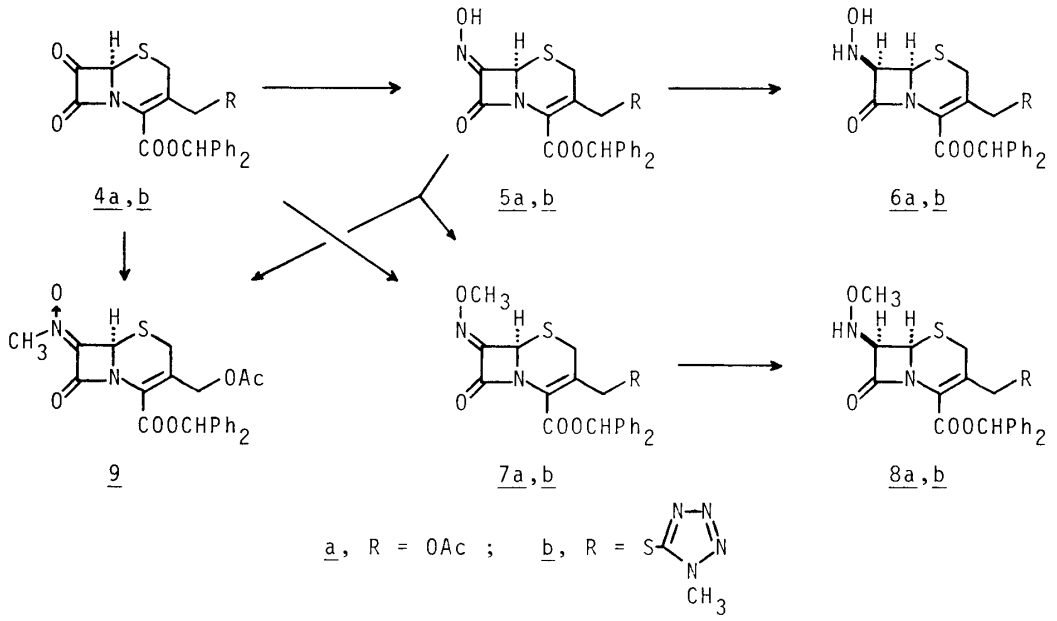
3

reactivity of its adjacent β-lactam carbonyl. In this connection, we were also interested in preparing the corresponding methoxyamide derivatives (e.g. 3) to compare their activity with that of the hydroxyamides. Here we describe a method for synthesizing the cephalosporin model of such hydroxyamides 2 and methoxyamides 3.

When 7-oxocephem 4a, prepared as described in our preceding paper,[4] was allowed to react with hydroxylamine (1.8 equiv/CH_2Cl_2-DMF, room temperature, 4 h), a single oxime isomer 5a (mp 112-120°C)[5] was obtained in 88% yield. The configu-

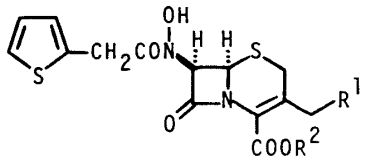
ration of the oxime group in 5a was considered to be Z as follows. Treatment of 5a with CH_2N_2 (Et_2O, 0°C → room temperature, 1 h) gave a mixture of methoxime 7a (mp 150-151°C)(see below) and nitrone 9 (oil) in a ratio of 3 : 5 (56% combined yield). In an NMR analysis (DMSO-d_6), 7a showed a 5% NOE between the methoxime methyl at δ 3.93 and the 6-proton at δ 5.38, thus suggesting the methoxime group in 7a and hence the oxime group in 5a both to be Z.[6] The structure of 9 was confirmed by direct comparison with the sample prepared by reaction of 4a with *N*-methylhydroxylamine (2 equiv/CH_2Cl_2-DMF, reflux, 3 h, 67%).

Reduction of 5a to the corresponding hydroxyamine 6a [mp 167-168°C(dec.)] was accomplished in 44% yield by using borane-pyridine (7N HCl/EtOH, 0°C → room temperature, 2 h),[7] which attacked from the less hindered α-face of the β-lactam nucleus to produce stereospecifically the cis configuration of 6a: in the NMR spectrum,[9] the newly formed C-7 proton was observed with cis coupling (J=4.5Hz) to the C-6 proton. A similar two-step sequence from 4b[4] provided 5b (mp 173-174°C) in 46% yield and then 6b [mp 168-169°C(dec.)] in 63% yield.

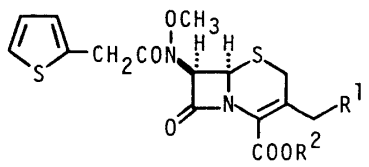


Meanwhile, the methoxime 7a obtained above was also prepared by treatment of 4a with methoxyamine in a manner similar to that used for 5a. This reaction likewise produced 7a, as the sole product, in 71% yield. Reduction of 7a using borane-THF (THF, 0°C → room temperature, 2 h) afforded 8a (mp 112-115°C) in 64% yield. Similarly, methoxime 7b [mp 209-212°C(dec.)], prepared as above from 4b in 43% yield, was reduced to 8b [mp 128-137°C(dec.)] in 51% yield.

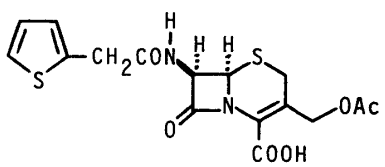
Acylation of each amine intermediate with 2-thienylacetyl chloride in the usual manner gave the corresponding N^7-acyl derivatives 10a,b and 12a,b (60, 42, 45, and 50% yields, respectively), which were followed by deprotection of the benzhydryl group by treatment with TFA (anisole/CH_2Cl_2, 0°C) to yield the carboxylic acids 11a,b and 13a,b (73, 65, 68, and 90% yields, respectively). The hydroxyamine derivatives 11a,b showed significant antibacterial activities against a standard



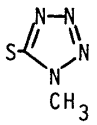
10a,b $R^2 = CHPh_2$
11a,b $R^2 = H$



12a,b $R^2 = CHPh_2$
13a,b $R^2 = H$



14

a $R^1 = OAc$; b $R^2 =$ 

series of laboratory strains, though slightly less than the reference compound 14.[8] It is interesting that the methoxyamine derivatives 13a,b also displayed activity of the same order as 11a,b and, in fact, were rather superior to 11a,b against certain microorganisms.[8] It is thus likely that the amido hydrogen of the traditional β-lactam antibiotics (e.g. 14) is not necessarily required for antibacterial activity.

We have demonstrated above a new synthetic method for the preparation of the cis *N*-substituted cephalosporin derivatives. With this kind of *N*-substituted cephalosporins, the corresponding trans stereochemistry may also be an attractive target in view of the outstanding activity of thienamycin having the trans C-6 side-chain.

REFERENCES AND NOTES

1) For a review on carbapenem antibiotics, see R. D. G. Cooper, "Topics in Antibiotic Chemistry", Vol. 3, ed. by P. G. Sammes, Ellis Horwood, Chichester, 1980, pp. 101-138.
2) (a) F. Dininno, T. R. Beatie, and B. G. Christensen, J. Org. Chem. 42, 2960 (1977); (b) H. E. Applegate, C. M. Cimarusti, and W. A. Slusarchyk, Tetrahedron Lett., 1637 (1979).
3) D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, J. Am. Chem. Soc., 100, 313 (1978).
4) D. Hagiwara, K. Sawada, T. Ohnami, M. Aratani, and M. Hashimoto, J. C. S. Chem. Commun., 578 (1982).
5) This and all subsequently described new compounds were characterized by their spectral data. Selected data are shown in ref 9.
6) Y. Morimoto et al. in our laboratories had observed that the E isomer of ceftizoxime, 7β-[(Z)-2-methoxyimino-2-(2-amino-4-thiazolyl)acetamido]-3-cephem-4-carboxylic acid, shows an NOE (about 10%) between the methoxime methyl and the 5-proton of the aminothiazole ring, while ceftizoxime itself shows no significant NOE: unpublished results.
7) (a) H. Feuer, B. F. Vincent, Jr., and R. S. Bartlett, J. Org. Chem., 30, 2877 (1965); (b) Y. Kikugawa and M. Kawase, J. Chem. Soc. Perkin I, 643 (1979).

8) Details will be reported in a full paper.

9) 5a: ν ($CHCl_3$) 1785 cm^{-1}; δ ($CDCl_3$) 1.97 (s, 3H), 3.40 (ABq, J=18Hz, 2H), 4.85 (ABq, J=13Hz, 2H), 5.38 (s, 1H). 5b: ν (nujol) 1775 cm^{-1}; δ (DMSO-d_6) 3.88 (ABq, J=18Hz, 2H), 3.90 (s, 3H), 4.28 (ABq, 14Hz, 2H), 5.78 (s, 1H), 13.13 (s, 1H). 6a: ν (nujol) 1760 cm^{-1}; δ (DMSO-d_6) 1.96 (s, 3H), 3.53 (ABq, J=16Hz, 2H), 4.69 (ABq, J=13Hz, 2H), 4.9-5.1 (m, 2H), 6.43 (dd, J=1.5, 4.5Hz, 1H), 7.70 (d, J=1.5Hz, 1H). 6b: ν (nujol) 1780 cm^{-1}; δ (DMSO-d_6+D_2O) 3.67 (br s, 2H), 3.87 (s, 3H), 4.22 (ABq, J=13Hz, 2H), 4.97 (d, J=5Hz, 1H), 5.06 (d, J=5Hz, 1H). 7a: ν (nujol) 1790 cm^{-1}; δ ($CDCl_3$) 2.00 (s, 3H), 3.47 (ABq, J=18Hz, 2H), 4.10 (s, 3H), 4.88 (ABq, J=14Hz, 2H), 5.37 (s, 1H). 7b: ν (nujol) 1780 cm^{-1}; δ (DMSO-d_6) 3.84 (ABq, J=19Hz, 2H), 3.91 (s, 3H), 4.08 (s, 3H), 4.30 (ABq, J=14Hz, 2H), 5.84 (s, 1H). 8a: ν (nujol) 1790 cm^{-1}; δ (DMSO-d_6) 1.97 (s, 3H), 3.44 (s, 3H), 3.55 (ABq, J=20Hz, 2H), 4.70 (ABq, J=12Hz, 2H), 5.08 (s, 2H). 8b: ν (CH_2Cl_2) 1780 cm^{-1}; δ ($CDCl_3$) 3.58 (s, 3H), 3.72 (s, 2H), 3.82 (s, 3H), 4.34 (ABq, J=14Hz, 2H), 4.96 (br signal, 1H), 6.10 (br signal, 1H). 9: ν ($CHCl_3$) 1780 cm^{-1}; δ ($CDCl_3$) 2.00 (s, 3H), 3.46 (ABq, J=18Hz, 2H), 3.97 (s, 3H), 4.88 (ABq, J=14Hz, 2H), 5.53 (s, 1H). 10a: ν ($CHCl_3$) 1780 cm^{-1}; δ ($CDCl_3$) 2.03 (s, 3H), 3.43 (br s, 2H), 4.07 (s, 2H), 4.97 (ABq, J=14Hz, 2H), 4.99 (d, J=5Hz, 1H), 6.03 (d, J=5Hz, 1H), 7.80 (s, 1H). 10b: ν ($CHCl_3$) 1785 cm^{-1}; δ ($CDCl_3$) 3.60 (ABq, J=18Hz, 2H), 3.78 (s, 3H), 4.05 (s, 2H), 4.31 (ABq, J=14Hz, 2H), 4.95 (d, J=5Hz, 1H), 6.02 (d, J=5Hz, 1H). 11a: ν (KBr) 1750 cm^{-1}; δ (DMSO-d_6) 2.01 (s, 3H), 3.38 (ABq, J=17Hz, 2H), 4.08 (s, 2H), 4.92 (ABq, J=12Hz, 2H), 5.02 (d, J=5Hz, 1H), 5.97 (d, J=5Hz, 1H). 11b: ν (nujol) 1780 cm^{-1}; δ (DMSO-d_6) 3.60 (s, 2H), 3.90 (s, 3H), 4.00 (s, 2H), 4.30 (ABq, J=13Hz, 2H), 5.07 (d, J=5Hz, 1H), 6.10 (d, J=5Hz, 1H). 12a: ν (CH_2Cl_2) 1790 cm^{-1}; δ ($CDCl_3$) 2.04 s, 3H), 3.38 (s, 2H), 3.96 (s, 2H), 4.13 (s, 2H), 5.00 (d, J=4Hz, 1H), 5.01 ABq, J=14Hz, 2H), 5.90 (d, J=4Hz, 1H). 12b: ν (CH_2Cl_2) 1785 cm^{-1}; δ ($CDCl_3$) 3.61 (s, 2H), 3.85 (s, 3H), 3.94 (s, 3H), 4.12 (s, 2H), 4.45 (ABq, J=14Hz, 2H), 5.00 (d, J=4Hz, 1H), 5.89 (d, J=4Hz, 1H). 13a (Na salt): ν (nujol) 1760 cm^{-1}; δ (D_2O) 2.14 (s, 3H), 3.48 (ABq, J=19Hz, 2H), 3.94 (s, 3H), 4.20 (s, 2H), 4.96 (ABq, J=14Hz, 2H), 5.13 (d, J=4Hz, 1H), 5.89 (d, J=4Hz, 1H). 13b: ν (nujol) 1780 cm^{-1}; δ (DMSO-d_6) 3.60 (br s, 2H), 3.80 (s, 3H), 3.92 (s, 3H), 4.10 (ABq, J=13Hz, 2H), 5.06 (d, J=4Hz, 1H), 5.97 (d, J=4Hz, 1H).

(Received July 12, 1982)