# SYNTHESIS OF 7-HYDRAZINOCEPHALOSPORINS

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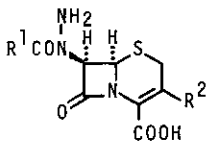
Abstract: Hydrazonation of 7-oxocephems 2a,b, followed by borane reduction of the resulting E and Z hydrazono compounds 3a,b and 4a,b, provided the key intermediates 5a,b, which were acylated to 6a,b and then deprotected to yield the 7-hydrazinocephalosporin derivatives 7a,b.

The remarkable biological property of the carbapenem antibiotics represented by thienamycin[1] has stimulated considerable interest in preparing penicillin and cephalosporin analogues carrying at C-6(7) hydroxyalkyl chains rather than the traditional amidic substituents[2]. Furthermore, the discovery of these new antibiotics has also aroused a renewed interest in chemically modifying the amide function of penicillins and cephalosporins[3]. We described in the preceding paper the preparation of some $N^7$-substituted cephalosporin derivatives[4]. Herein we report the synthesis of the 7-hydrazinocephalosporins (1)[5] by a synthetic approach similar to that described before[4].

Reaction of 2a[7] with t-butyl carbazate (1.1 equiv) in the presence of pyridine hydrochloride (1.5 equiv) in chloroform at reflux (30 min) with removing water by using molecular sieves produced a mixture of the geometric isomers 3a and 4a in a ratio of 3 : 1. The mixture was easily separated by silica gel chromatography into pure samples of each isomer[9] in 44% and 12% yields, respectively. The configuration of the hydrazono group in the major isomer 3a was assigned to be syn to the β-lactam carbonyl based on the observed lower β-lactam carbonyl frequency (1760 $cm^{-1}$) in the IR spectrum ($CHCl_3$) of 3a as compared to its counterpart 4a (1790 $cm^{-1}$). This 30 $cm^{-1}$ lower shift of the frequency of 3a suggests the presence of an internal hydrogen bonding between the hydrazone hydrogen and the β-lactam carbonyl oxygen in 3a.

Reduction of this major isomer 3a with borane-tetrahydrofuran complex in tetrahydrofuran at 0°C afforded in 83% yield hydrazino compound 5a, in which the newly



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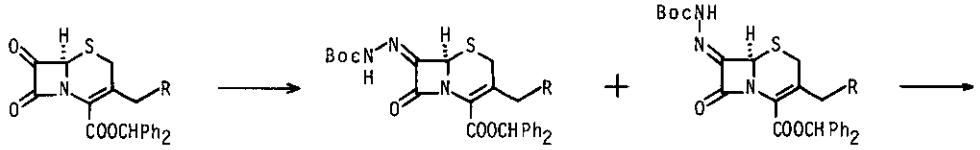

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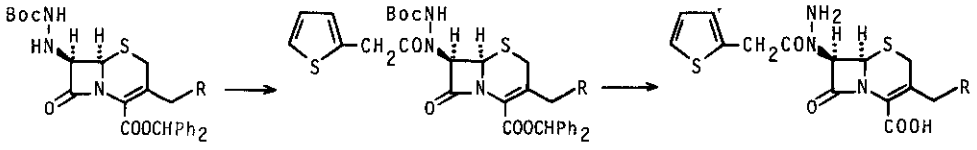

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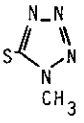
a, R = OAc; b, R = 

introduced C-7 proton was observed with cis coupling (J=4Hz) to the C-6 proton in the NMR spectrum[9], suggesting the β-configuration of the hydrazino group in 5a. A similar reduction of the minor isomer 4a also produced the same product 5a in 79% yield. It thus proved unnecessary to separate the mixture of 3a and 4a. Indeed, on reduction as above of the mixture (3a and 4a) obtained in another run in 72% yield after a brief chromatography, the desired product 5a was secured in 75% yield. It is noteworthy that, on these reductions, there was no detectable amount of the diastereomeric α-isomer. This can be ascribed to the steric hindrance of the substrates: the reagent would approach from the less hindered α-face of the β-lactam nuclei.

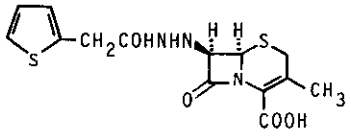
A similar sequence of reactions from 7-oxocephem 2b[7] also provided, via 3b and 4b (47%), 5b (71%).

Acylation of 5a and 5b with 2-thienylacetyl chloride in the usual manner gave 6a and 6b, which were followed by removal of the benzhydryl and t-butoxycarbonyl

protecting groups to yield 7a and 7b, respectively. These materials, however, were found to possess no significant antibacterial activity.

REFERENCES AND NOTES


1. G. Albers-Schonberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, E. M. Kahan, R. F. Ratcliffe, E. Walton, L. T. Ruswinkle, R. B. Morin, and B. G. Christensen, J. Am. Chem. Soc. 100, 6491 (1978).
2. (a) F. DiNinno, T. R. Beattie, and B. G. Christensen, J. Org. Chem. 42, 2960 (1977). (b) H. E. Applegate, C. M. Cimarsti, and W. A. Slusarchyk, Tetrahedron Lett. 1637 (1979).
3. For a review on the up-to-date amidic side-chain variations, see F. A. Jung, W. R. Pilgrim, J. P. Poyser, and P. J. Siret, "Topics in Antibiotic Chemistry", Vol. 4, P. G. Sammes, Ed., Ellis Horwood, Chichester, 1980, pp218-241.
4. D. Hagiwara, K. Sawada, T. Ohnami, and M. Hashimoto, Tetrahedron Lett. submitted for publication.
5. The isomeric hydrazino compound i has earlier been prepared by Sheehan et al[6].



i

6. J. C. Sheehan, Y. S. Lo, and D. R. Ponzi, J. Org. Chem. 42, 1012 (1977).
7. The starting materials 2a and 2b were prepared as described in our previous paper[8].
8. D. Hagiwara, K. Sawada, T. Ohnami, M. Aratani, and M. Hashimoto, J. C. S. Chem. Comm. in press.
9. This and all subsequently described compounds were characterized by their physical properties. Selected data are as follows.

3a: mp 95-100°C; ν($CHCl_3$) 1760(sh), 1740 $cm^{-1}$; δ(DMSO-$d_6$) 1.97(s, 3H), 3.67(br s, 3H), 4.78(ABq, J=14Hz, 2H), 5.63(s, 1H), 11.00(s, 1H). 4a: mp 99-102°C; ν($CHCl_3$) 1790, 1730 $cm^{-1}$; δ(DMSO-$d_6$) 2.00(s, 3H), 3.58(br s, 2H), 4.82(ABq, J=13Hz, 2H), 5.63(s, 1H), 11.53(s, 1H). 3b: mp 148-150°C; ν($CHCl_3$) 1760, 1750, 1720 $cm^{-1}$; δ(DMSO-$d_6$) 3.82(s, 2H), 3.83(s, 3H), 4.35(ABq, J=13Hz, 2H), 5.28(s, 1H), 9.27(s, 1H). 4b: mp 146-148°C dec; ν($CHCl_3$) 1790, 1750, 1720 $cm^{-1}$; δ(DMSO-$d_6$) 3.68(br s, 2H), 3.86(s, 3H), 4.33(ABq, J=14Hz, 2H), 5.58(s, 1H), 11.47(s, 1H). 5a: mp 146-148°C; ν(nujol) 1785, 1725, 1710, 1695 $cm^{-1}$; δ($CDCl_3$) 2.00(s, 3H), 3.42(ABq, J=17Hz, 2H), 4.58(d, J=4Hz, 1H), 4.7-5.1(m, 4H), 6.34 (d, J=4Hz, 1H). 5b: oil; ν($CHCl_3$) 3.73(br s, 2H), 3.87(s, 3H), 4.38(ABq, J=14Hz, 1H), 4.62(d, J=4Hz, 1H), 4.93(d, J=5Hz, 1H), 4.97(d, J=5Hz, 1H), 6.25(d, J=4Hz, 1H). 6a: oil; ν($CHCl_3$) 1790 $cm^{-1}$; δ($CDCl_3$) 1.97(s, 3H), 3.40(br s, 2H), 3.95(ABq, J=10Hz, 2H), 4.87(ABq, J=13Hz, 2H), 4.92(d, J=5Hz, 1H), 5.97(d, J=5Hz, 1H). 6b: oil; ν($CHCl_3$) 1790 $cm^{-1}$; δ($CDCl_3$) 3.70(br s, 2H), 3.80(s, 3H), 3.97(ABq, J=10Hz, 2H), 4.33(ABq, J=14Hz, 2H), 4.95(d, J=5Hz, 1H), 5.98(d, J=5Hz, 1H). 7a: powder; ν(nujol) 1760-1740 $cm^{-1}$; δ($CD_3OD$) 2.06(s, 3H), 3.35 (ABq, J=18Hz, 2H), 4.16(s, 2H), 4.88(br s, 2H), 5.10(d, J=5Hz, 1H), 5.98(d, J=5Hz, 1H). 7b: mp 133-140°C; ν(nujol) 1770-1730 $cm^{-1}$; δ(DMSO-$d_6$) 3.50(br s, 2H), 3.90(s, 3H), 4.90(d, J=5Hz, 1H), 5.85(d, J=5Hz, 1H).

Received, 5th April, 1982