# SYNTHESIS OF (6R, 7R)-PHENYLACETYLMETHYL-3-(1-METHYL-1H-TETRAZOL-5-YL)THIOMETHYL-1-OXA-1-DETHIACEPHALOSPORANIC ACID†

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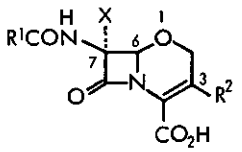
Abstract — Synthesis of the title compound 8 from the 7α-methoxy, 7β-amino-1-oxacephem 3, involving stereocontrolled reduction of the 7-phenylacetylmethylene derivatives 6 to 7β-phenylacetylmethyl derivative 7, is described.

1-Oxacephem antibiotics 1, in which compound 2 (6059-S) is representative, have recently attracted much attention because of their more favourable antibacterial activity than that of cephalosporins.[1] As a part of our continuing work on 1-oxacephems, we have prepared the title compound 8, in which the nitrogen atom at C-7 of the corresponding 1-oxacephem antibiotics is replaced by carbon (methylene), for biological evaluation.

7-Oxo-1-oxacephem 4, which exists as the hydrated form,[2] was prepared in good yield from methoxy-amine 3,[1] the nucleus of 2, on brief treatment with perchloric acid in a mixture of water, acetone, and tetrahydrofuran at room temperature. Recent development of a stereocontrolled and straightforward 1-oxacephem synthesis in our laboratories[3] has made the methoxyamine 3 readily available in quantity. The 7-oxo compound 4 reacted smoothly with Wittig reagent 5 at 0° in methylene dichloride, giving a stereoisomeric mixture of conjugated ketones 6 in good yield (90% from 3). Stereoselective reduction of both the exo double bonds (E and Z) in 6 to 7β-phenylacetylmethyl derivative 7[4] was conveniently achieved in a yield of 35% by zinc-acetic acid reduction in methylene dichloride under ice-cooling. The 7α-isomer was not detected in this reaction. The low yield of 7 may be attributed to a partial reductive elimination of the methyltetrazolylmercapto group during the course of the reaction. In fact when this reduction procedure was applied to 3-methylcephem derivatives 9 (stereoisomeric mixture), prepared similarly from the corresponding 7-oxocephem



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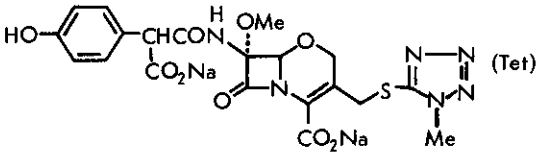
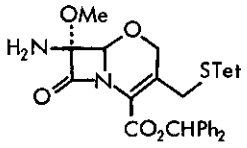


2 (6059-S)



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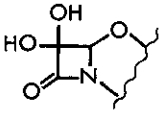

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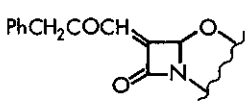

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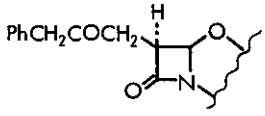

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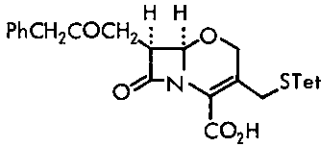

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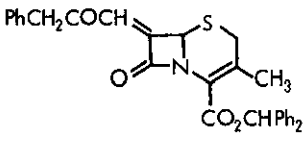

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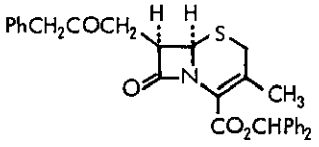

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compound, only the 7β-substituted product 10 was obtained in a good yield of 70%. Deesterification of 7 with trifluoroacetic acid and anisole gave the title compound 8.[4]

Biological activity of 8 was found to be disappointingly low compared to that of the 7β-phenylacetamido analog, and therefore no further work along this line was pursued.

REFERENCES AND NOTES

† Dedicated to Prof. Hamao Umezawa on the occasion of his 65th birthday.

1. M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem., 1979, 22, 757.

2. Hydrogen bonding between 7β-OH and 1-oxygen in 4 seems to stabilize the hydrated form.

3. a) S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, J. Am. Chem. Soc., 1979, 101, 4403; b) M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, submitted to J. Am. Chem. Soc.

4. 7 IR ($CHCl_3$): 1785, 1715 $cm^{-1}$, NMR ($CDCl_3$) δ: 2.73-2.95 (m, 2H, $-CH_2CO$), 3.68 (s, 2H, $PhCH_2-$), 3.75 (s, 3H, $N-CH_3$), 3.8-4.2 (m, 1H, $C_7-H$), 4.21 (s, 2H, $-CH_2-STet$), 4.5 (bs, 2H, $OCH_2-$), 4.98 (d, 1H, J = 4 Hz, $C_6-H$), 6.88 (s, 1H, $-CHPh_2$), 7.0-7.60 (m, 15H, aromatic). 8 IR ($CHCl_3$): 3600-2400, 1782, 1718 $cm^{-1}$.

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