SYNTHESIS OF (±)-OXADETHIA-2,3-BENZOCEPHEMS

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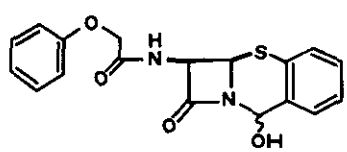
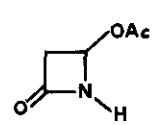
Abstract — The new 1-oxadethia-2,3-benzocephem ring system has been obtained by a one step synthesis from the readily available 4-acetoxyazetidin-2-one (2).

Recently, several types of biologically active 1-oxadethia analogues of cephalosporins have been prepared.[1] On the other hand, Sheehan et al synthesized a cephem (1) which was shown to have significant biological activity.[2] We now wish to report a simple synthesis of the title compounds[3], which possess a novel 1-oxadethia-2-cephem ring system.

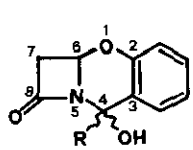
Readily available (±)-4-acetoxyazetidin-2-one (2)[4] was condensed with salicylaldehyde in aqueous sodium hydroxide to give, in nearly quantitative yield, (3a)[5], mp 136-137°, ν_{max} ($CHCl_3$) 3575, 3340 (OH), and 1778 cm^{-1} (β-lactam C=O), δ ($CDCl_3$) 3.00 (1H, d, J 16 Hz, C_7-H), 3.31 (1H, dd, J 16 and 3 Hz, C_7-H), 4.95 (1H, d, J 5.5 Hz, OH), 5.30 (1H, d, J 3 Hz, C_6-H), 5.83 (1H, d, 5.5 Hz, C_4-H), and 6.86-7.26 (4H, m, ArH). Similarly, (2) reacted with o-hydroxyacetophenone to give, in 76 % yield, (4a)[5], mp 119-120°, ν_{max} ($CHCl_3$) 3575, 3340 (OH), and 1775 cm^{-1} (β-lactam C=O), δ ($CDCl_3$) 1.93 (3H, s, $-CH_3$), 3.00 (1H, dd, J 15.5 and 2 Hz, C_7-H), 3.20 (1H, dd,



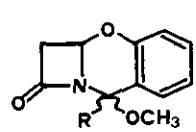
(1)



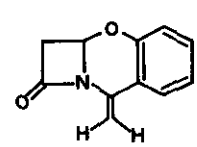
(2)



(3a) R= H
(4a) R= CH_3



(3b) R= H
(4b) R= CH_3



(5)

J 15.5 and 3 Hz, C_7-H), 4.20 (1H, s, OH), 5.24 (1H, dd, J 2 and 3 Hz, C_6-H), and 6.88-7.53 (4H, m, ArH). The hydroxy group of (3a) and (4a) shows a general reactivity as carbinolamide. For example, methanolysis (methanol, p-toluenesulphonic acid) of (3a) and (4a) gave (3b) (90 %), mp 88-89°, and (4b) (85 %), mp 110-111°, respectively. Treatment of (4a) with thionyl chloride in dichloromethane at -15° in the presence of triethylamine gave the enamide (5) in 75 % yield, ν_{max} ($CHCl_3$) 1778 (β-lactam C=O), and 1635 cm^{-1} (C=C), δ ($CDCl_3$) 5.12 (1H, d, J 1.5 Hz, C=CH), and 5.15 (1H, d, J 1.5 Hz, C=CH), which promises a variety of functionalization at C-4 position.

REFERENCES

1. M. Narisada, H. Onoue, and W. Nagata, Heterocycles, 1977, 7, 839; L. D. Cama, and B. G. Christensen, J. Amer. Chem. Soc., 1974, 96, 7582; R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Pastel and B. G. Christensen, J. Med. Chem., 1977, 20, 551.
2. J. C. Sheehan, H. C. Dalzell, J. M. Greenwood, and D. R. Ponzi, J. Org. Chem., 1974, 39, 277.
3. Satisfactory analytical and spectroscopic data were obtained for all new compounds. All new compounds herein reported were obtained as single products. The relative stereochemistry of them is under investigation.
4. K. Clauss, D. Grimm, and G. Prossel, Annalen, 1974, 539.
5. The numbering, shown in (3a) and (4a), follows that used in penicillins.

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