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A SHORT SYNTHESIS OF 7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPTANE. A BASIC SKELETON OF PENICILLIN-TYPE ß-LACTAMS

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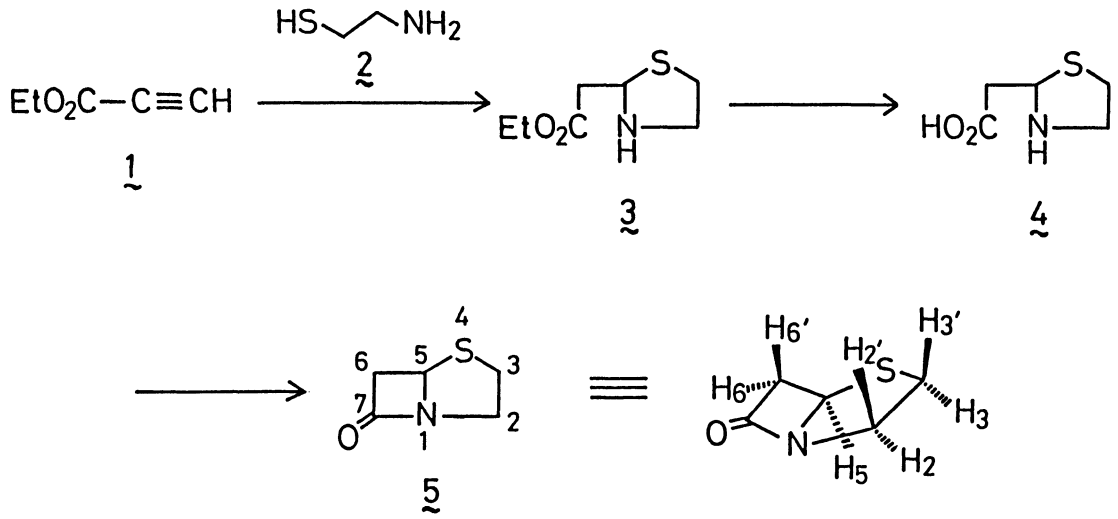
7-Oxo-4-thia-1-azabicyclo[3.2.0]heptane, a basic skeleton of penicillins, was synthesized for the first time from ethyl propiolate in three steps. The key step was the formation of ß-lactam ring of thiazolidine-2-acetic acid by the use of Mukaiyama-Ohno's method.

Penicillin-type ß-lactams are characterized by structure (5) termed as "penam"; many derivatives have been synthesized and their physical and biological properties tested. Though 1-azabicyclo[3.2.0]heptan-7-one, a basic skeleton of carbocyclic analogues of penicillins has been synthesized and its inherent instability disclosed,[1] the parent compound of penams has not yet been synthesized. We describe here our result on the synthesis of this basic skeletal compound (5) starting from ethyl propiolate and cysteamine.

Ethyl thiazolidine-2-acetate (3)[2] was prepared in 65% yield by reacting equimolar amounts of ethyl propiolate (1), cysteamine hydrochloride (2-HCl), and triethylamine in ethanol (room temp, 10 h). Acid hydrolysis of 3 (concentrated hydrochloric acid, room temp, 2 h) afforded thiazolidine-2-acetic acid hydrochloride (4-HCl; mp 103-105 °C) in 47% yield.

While many methods had been applied to either 3 or 4 to effect the ß-lactam formation,[3] only the use of Mukaiyama-Ohno's method[4,5] to the acid 4 gave the desired ß-lactam 5. Thus, treatment of the hydrochloride of 4 (0.01 M solution) with triphenylphosphine (1.2 mol equiv.) and 2,2-dipyridyl disulfide (1.2 mol equiv.) in acetonitrile in the presence of a slight excess (1.1 mol equiv.) of triethylamine at 0 °C for 3 h gave, after silica gel column chromatography (hexane-ethyl acetate, 10:1), 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane [5, colorless oil; IR ($CHCl_3$): 1770 cm^{-1}; high resolution MS *m/z* Calcd. for C_5H_7NOS (M^+): 129.0248. Found: 129.0272] in 8% yield. Dilution of 4 to 0.002 M in the above reaction resulted only in a slight increase of the yield of 5 (9%). The other products in these reactions were intractable oils with high polarity, whose IR spectra revealed only an amide carbonyl band (*ca.* 1630 cm^{-1}) in its carbonyl region. The structure of 5 was further confirmed by ^{1}H-NMR spectrum ($CDCl_3$) δ: 4.92 (1H, dd, $J_{5,6}$=4.0 Hz, $J_{5,6'}$=2.0 Hz, H_5), 4.15 (1H, ddd, $J_{2,2'}$=11.5 Hz, $J_{2',3(or\ 3')}$=4.0 Hz, $J_{2',3'(or\ 3)}$=6.0 Hz, $H_{2'}$), 3.95 (1H, ddd, $J_{6,6'}$=16.0 Hz, $J_{5,6}$=4.0 Hz, $J_{6,3(or\ 3')}$=1.0 Hz, H_6), 3.50 (1H, dd, $J_{5,6'}$=2.0 Hz, $J_{6',6}$=16.0 Hz, $H_{6'}$).

The compound 5 thus obtained is stable both in its pure state and in ordinary organic solvents and can be stored indefinitely. Thus, we have now



accomplished the first synthesis of 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (5), the so-called penam *via* three steps from readily available materials (1 and 2).

The present method not only demonstrates the chemical stability of the skeletal compound (5) of penams, but also may open a new and simple route to penams having substituents at 5- (use of 3-substituted propiolic acid esters), 2- and/or 3-positions (use of substituted cysteamines) as well as the corresponding cephams (use of homocysteamine and its derivatives).[6)]

References

1) Synthesis and inherent instability of 1-azabicyclo[3.2.0]heptan-7-one (the basic skeleton of carbocyclic analogues of penicillins) were reported: a) for a racemic form; F. Moll, *Z. Naturforsch.*, *B*, 24, 942 (1969); b) for an optically active form; R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 43, 4438 (1978).

2) All compounds had correct elemental analyses and were supported by acceptable spectral data.

3) Following β-lactam formation reactions have so far been applied either to 3 or 4; i) Grignard reagents to 3, ii) dehydration of 4 by DCC, iii) cyclization of 4 by treatment with $SOCl_2$ followed by Et_3N.

4) Mukaiyama's reagent, Ph_3P-$(PyS)_2$, was originally used for peptide synthesis using CH_2Cl_2 or DMF as solvent: a) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1970, 1901; b) T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, 15, 94 (1976).

5) Ohno *et al.* used this reagent for the formation of β-lactam compounds from β-amino acids and found acetonitrile as a solvent of choice for this reaction: S. Kobayashi, T. Iimori, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, 103, 2406 (1981).

6) Generally, irrespective of the kinds of reagents employed, the yields of β-lactams from β-amino acids (or their esters) decrease markedly as the number of substituents on the carboxymethyl side chain decreases; J. C. Sheehan and E. J. Corey, "Organic Reactions," ed by R. Adams, John Wiley and Sons, Inc., New York (1957), Vol. 9, p.388.

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