Penicillin-Cephalosporin Conversion. VII. An Improved Synthesis of 3-Methylenecephams

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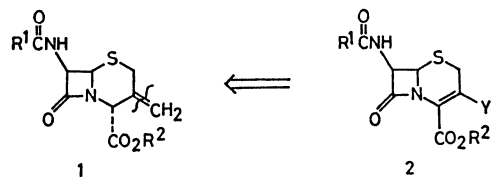
Synopsis. Efficient conversion of 2-(7-oxo-2,6-diaza-4-thiabicyclo[3.2.0]hept-2-en-6-yl)-3-chloromethyl-3-butenoates (**4**), derived from natural penicillins, into 3-methylenecephams (**1**) has been performed by a simple two-step operation, which comprises replacement of the allylic chlorine atom of **4** with iodine and subsequent acid-catalyzed hydrolysis, leading to **1** in 70—54% overall yields. In the latter step, the ring opening of the thiazoline moiety and the intramolecular substitution of the iodide with the thiol group proceed simultaneously.

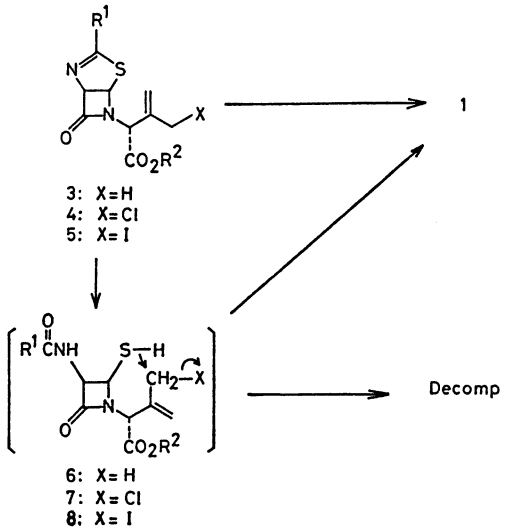
3-Methylenecephams **1** are important intermediates for the synthesis of useful cephalosporin antibiotics **2**, bearing an electronegative substituent, *e.g.*, halogen atom and methoxyl group, directly attached to the C-3 position.[1] These have been prepared by either reductive elimination of the acetoxyl group of 3-acetoxymethylcephalosporins[2] or chemical conversion of penicillins.[3] In connection with the current interest in the penicillin-cephalosporin conversion,[4] considerable efforts have been made to develop a significant route to **1** from natural penicillins.

In the preceding communication,[5] we disclosed electrolytic ene-type chlorination of thiazoline-azetidinones **3** derived from penicillins, providing 2-(7-oxo-2,6-diaza-4-thiabicyclo[3.2.0]hept-2-en-6-yl)-3-chloromethyl-3-butenoates **4**, which can be expected to be a good precursor of the 3-methylenecephams **1**. In fact, the conversion of **4** to **1** has been carried out by treatment with $AgClO_4$ in dioxane,[3a] although the yields are not satisfactory.[6] The insufficient yields in a practical sense and use of a stoichiometric amount of the expensive silver salt prompted us to find out a new and more efficient method for this purpose. We now report a convenient two-step conversion of **4** to **1** which comprises replacement of chlorine atom of **4** with iodine and subsequent acid-catalyzed hydrolysis of the thiazoline ring of **5**, leading to the desired 3-methylenecephams **1** via the intermediate **8** (Scheme 2).

It has been demonstrated that the hydrolysis of the thiazoline ring of **3** in aqueous acidic media affords thiol **6** in high yields.[7] Thus, the hydrolysis of **4** to the thiol **7** followed by the ring closure by the intramolecular nucleophilic substitution of the allylic chlorine atom with the mercapto group seemed to be a straightforward route to **1**. At first, we investigated this possibility since no such conversion has yet been realized. Hydrolysis of **4a** ($R^1=PhCH_2$; $R^2=CH_3$) in aqueous 30% $HClO_4$–acetone–CH_2Cl_2 (0.2:1:1) proceeded smoothly to afford the thiol **7a** ($R^1=PhCH_2$; $R^2=CH_3$). The ring closure of **7a** was attempted with base, *e.g.*, NaH, Na_2CO_3, pyridine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under various conditions. But all attempts brought about a complex mixture of the decomposition products of **7a** and



Scheme 1.



Scheme 2.

failed in obtaining the desired product **1**.

These failure made us believe that the allylic chloride is not reactive enough for this cyclization. Consequently, we tried to use iodide **5** in place of chloride **4**. The iodide **5a** ($R^1=PhCH_2$; $R^2=CH_3$) was readily prepared from **4a** by heating with NaI in acetone. Then, hydrolysis of **5a** in methanol–CH_2Cl_2 (3/1) containing aqueous 5% HCl at room temperature afforded the desired 3-methylenecepham **1a** (70% yield). Although thiol **8a** ($R^1=PhCH_2$; $R^2=CH_3$) could not be detected in the reaction mixture, the ring closure would proceed via **8a** at room temperature without using any base due to the high reactivity of the iodide **8a**. With regard to the acid hydrolysis (**5a**→**1a**), an aqueous 5% HCl–methanol–CH_2Cl_2 system was found to be most effective among the following systems (yields of **1a**): aqueous 5% HCl–methanol (60%); aqueous 30% $HClO_4$–methanol (43%), aqueous 10% H_2SO_4–methanol (43%); aqueous 5% HCl–acetone (39%).

The conversion of **4** to **1** could be also performed by one-pot reaction without isolation of the intermediates **5**. Thus, after iodization of **4** with NaI in refluxing acetone, the reaction mixture was concentrated and the residue was treated with aqueous 5% HCl–methanol–CH_2Cl_2, affording **1** in 57—70% yields.

Experimental

IR spectra were determined on a JASCO IRA-I grating infrared spectrometer. ^{1}H NMR spectra were recorded at 60 M Hz with a Hitachi R-24 spectrometer and chemical shifts are reported in parts per million (δ) relative to $(CH_3)_4Si$ ($\delta=0.0$ ppm) as an internal standard. 2-(7-oxo-2,6-diaza-4-thiabicyclo[3.2.0]hept-2-en-6-yl)-3-chloromethyl-3-butenoates **4** were prepared by the electrolytic ene-type chlorination[5] of thiazoline-azetidinones **3**. Authentic samples of 3-methylenecephams **1** were obtained by the reported procedure.[3]

Hydrolysis of ***4a*** *($R^1=PhCH_2$; $R^2=CH_3$)* A mixture of **4a** (59 mg, 0.16 mmol) in acetone (1 ml) and CH_2Cl_2 (1 ml) containing aqueous 30% $HClO_4$ (0.2 ml) was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2 washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*, affording forms **7a** ($R^1=PhCH_2$; $R^2=CH_3$, 61 mg),[8] essentially homogeneous on TLC analysis: $R_f=0.05$ (SiO_2; benzene/AcOEt, 4/1). Without further purification,[9] the crude products were treated with DBU (5 μl) in *N,N*-dimethylformamide (1 ml) at -30 °C for 5 h. Usual work-up gave a complex mixture and any detectable amount of 3-methylenecepham **1a** ($R^1=PhCH_2$; $R^2=CH_3$) could not be observed on TLC analysis.

Conversion of ***4*** *to* ***1***. *Procedure A*: A mixture of **4a** ($R^1=PhCH_2$; $R^2=CH_3$, 376 mg, 1.03 mmol) and NaI (230 mg, 1.53 mmol) in acetone (10 ml) was heated to reflux for 3 h. The mixture was diluted with water (5 ml) and extracted with AcOEt. Usual work-up followed by column chromatography (SiO_2, hexane/AcOEt, 4/1) afforded iodide **5a** ($R^1=PhCH_2$; $R^2=CH_3$, 425 mg, 90%): ^{1}H NMR ($CDCl_3$) δ 3.62 (2H, s, CH_2I), 3.74 (3H, s, CH_3O), 3.87 (2H, s, CH_2Ph), 5.04 (1H, s), 5.45 (1H, s), 5.91 (2H, br s), 7.27 (5H, s). Immediately after isolation of the product,[10] **5a** (59 mg, 0.13 mmol) was dissolved in methanol (0.5 ml) and CH_2Cl_2 (0.5 ml) containing aqueous 5% HCl (0.2 ml). After stirring for 15 h, usual work-up followed by column chromatography (SiO_2), benzene/AcOEt, 5/1) gave **1a** (R $=PhCH_2$; $R^2=CH_3$, 31 mg, 70%), which was identical in all respects with the authentic sample;[3c] IR ($CHCl_3$) 3385, 1770, 1744, 1678, 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.17, 3.61, (2H, AB q, $J=14$ Hz, CH_2S), 3.60 (2H, s, CH_2CO), 3.74 (3H, s, CH_3O), 5.05 (1H, s), 5.18 (2H, br s), 5.35 (1H, d, $J=4$ Hz, CH(6)), 5.62 (1H, dd, $J=4$ and 10 Hz, CH(7)), 6.43 (1H, d, $J=10$ Hz, NH), 7.28 (5H, s).

Procedure B: A mixture of **4a** (82 mg, 0.22 mmol) and NaI (39 mg, 0.26 mmol) in acetone (1 ml) was heated to reflux for 3 h. After removal of the solvent *in vacuo*, the residue was dissolved in methanol (1.5 ml) and CH_2Cl_2 (0.5 ml) containing aqueous 5% HCl (0.4 ml). After being stirred at room temperature for 8 h, usual work-up gave **1a** ($R^1=PhCH_2$; $R^2=CH_3$, 55 mg) in 70% yield after column chromatography (SiO_2, benzene/AcOEt, 5/1). The IR and ^{1}H NMR spectra were fully identical with those of the sample **1a** prepared above.

In a similar manner as described above, benzyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate (**1b**) ($R^1=PhOCH_2$; $R^2=PhCH_2$) was obtained from **4b** ($R^1=PhOCH_2$; $R^2=PhCH_2$) in 57% overall yield, which was identical in all respects with the authentic sample; IR ($CHCl_3$) 3385, 1770, 1738, 1689, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.18, 3.58 (2H, AB q, $J=14$ Hz, CH_2S), 4.50 (2H, s, OCH_2CO), 5.15 (4H, br s), 5.23 (1H, s), 5.39 (1H, d, $J=4.5$ Hz, HC(6)), 5.70 (1H, dd, $J=4.5$ Hz and 9.5 Hz, HC(7)), 6.7 -7.5 (6H, m), 7.31 (5H, s).

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6) Treatment of **4a** ($R^1=PhCH_2$; $R^2=CH_3$) with $AgClO_4$ (1—1.2 equiv.) in dioxane provided 5—30% yields of **1a**.

7) M. Narisada, H. Onoue, M. Ohtani, F. Watanabe, T. Okada, and W. Nagata, *Tetrahedron Lett.*, **1978**, 1755.

8) Tentatively assigned based on the spectral data: IR ($CHCl_3$) 3380, 1775, 1745, 1680, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90 (1H, br s), 3.63 (2H, s), 3.76 (3H, s), 4.18 (2H, s), 5.0—5.6 (5H, m), 7.28 (6H, br s).

9) Upon chromatography on a SiO_2 column, **7a** was decomposed even on a neutral SiO_2 (Mallinckrodt CC-7).

10) Iodide **5a** was unstable and gradually decomposed under standing in atmosphere.