BIS-TRIMETHYLSILYLCEFAMANDOLE: AN UNUSUALLY STABLE TRIMETHYLSILYL-INTERMEDIATE

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The preparation of crystalline bis-trimethylsilylcefamandole (**7**) and its utility in the preparation and purification of cefamandole are described. Although stable to solvolysis in isopropyl alcohol, **7** underwent smooth conversion to cefamandole in the presence of water, methanol, or ethanol.

Cefamandole (**1**), 7-D-(−)-mandelamido-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid, a semi-synthetic cephalosporin antibiotic, has been shown to be active *in vitro* against a wide variety of Gram-positive and Gram-negative organisms[1]. Particularly noteworthy is the activity of cefamandole against *Enterobacteriaceae* resistant to most clinically available cephalosporins[2].

The *in vitro* activity of cefamandole has been confirmed in many laboratories, and numerous reports concerning the clinical utility of cefamandole have appeared[3]. Because early attempts to prepare a stable crystalline form of cefamandole sodium were unsuccessful, the formyl ester of cefamandole (cefamandole nafate) was chosen for clinical evaluation[4]. Cefamandole nafate (**2b**) was recently made available for clinical use in the U.S. and Europe.

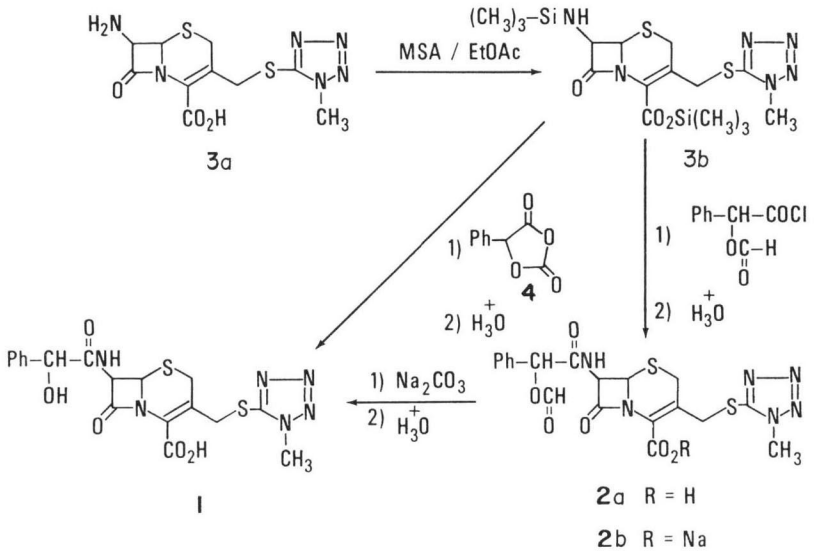
Chemistry

Cefamandole can be synthesized by acylation of 7-amino-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid (**3a**) derived from 7-aminocephalosporanic acid (7-ACA) with either anhydro-O-carboxymandelic acid (**4**) or O-formyl mandeloyl chloride, followed by base hydrolysis of the resulting formate ester **2a**[6] (Scheme 1). However, chromatographic purification of the product is necessary to obtain a pure crystalline product. In order to facilitate acylation of **3a** under non-aqueous conditions, **3a** is solubilized in organic solvents by silylation[7].

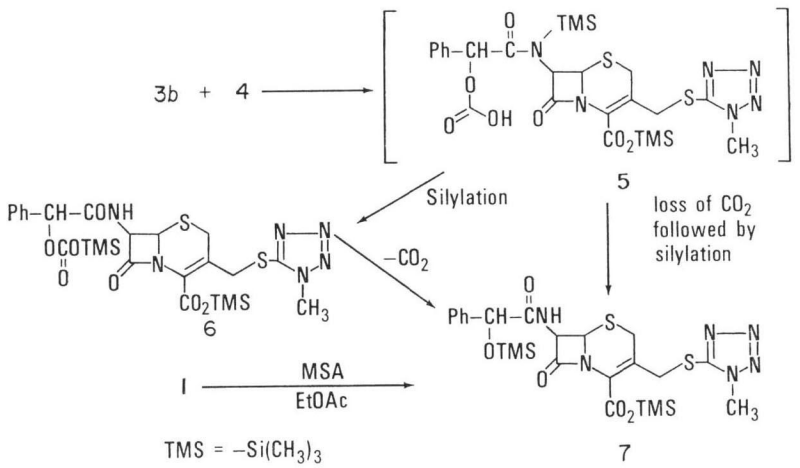
During the acylation of **3b** (prepared *in situ* by the silylation of **3a** with MSA) with **4**, a crystalline precipitate formed which was isolated by filtration. NMR and TLC (9: 1 acetone - HOAc and 4: 1 CH_3CN - H_2O) indicated that the material was a mixture of acetamide and cefamandole (or a derivative of cefamandole). The crystalline solid was washed with copious quantities of water and dried. Examination of the 100-MHz NMR spectrum of the washed solid indicated two additional resonances at δ 0.12 and 0.36 ppm. In addition, the resonances due to the hydroxyl and carboxyl groups of cefamandole were absent. It was apparent that the excess monotrimethylsilylacetamide had trapped either the intermediate hemi-carbonate **5** to form **6** or cefamandole to form **7** (Scheme 2).

Upon further examination, the evolution of CO_2 during acylation was apparent. In addition, the derivative obtained from the silylation of cefamandole was indistinguishable by NMR and X-ray diffraction from that derived from the acylation of **3b** with **4**. It is evident from these data that the compound

Scheme 1.



Scheme 2.



isolated is **7** in both cases; however, whether **7** arises from **6** or directly from **5** is not known.

Cefamandole (**1**) exists as several crystalline modifications, among them a 2-propanol solvate and several different hydrated forms[8]. In an effort to convert **7** to the 2-propanol solvate of **1**, **7** was dissolved in boiling 2-propanol, filtered, and allowed to crystallize. Surprisingly, **7** was recovered unchanged (the product exhibited the same X-ray diffraction pattern as the starting material) in 73% yield. When dissolved in isopropyl alcohol or ethanol in the presence of water or methanol, **7** was smoothly converted to solvated cefamandole of excellent purity and in good yield (80%).

Although the hydrolysis of trimethylsilyl esters is a facile process[9], the hydrolysis of trimethylsilyl ethers is often more difficult[10]. However, trimethylsilyl derivatives of alcohols are still too labile to be generally useful as synthetic intermediates[11]. The isolation of **7** permits the synthesis of pure crystalline **1** without having to resort to laborious chromatographic procedures. Conversion of cefamandole

to **7** and subsequent hydrolysis back to **1** have been used in the purification of large lots of impure cefamandole.

Experimental

The melting point is uncorrected. NMR spectra were determined on a Varian Associates HA-100 or A-60-A spectrometer. Mass spectra were recorded on a CEC Model 21-110 mass spectrometer. X-Ray powder patterns were determined on a Norelco XG-3000 X-ray powder diffraction spectrometer. Microanalyses were performed in the microanalytical laboratory of the Lilly Research Laboratories.

Trimethylsilyl 7-[D-(O-trimethylsilyl)-mandelamido]-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylate (**7**)

[A.] Cefamandole (4.0 g, 8.6 mmol) and N-trimethylsilylacetamide (MSA) (4.5 g, 34.4 mmol) were dissolved in EtOAc (50 ml) and stirred at room temperature. A white crystalline precipitate formed almost immediately. After stirring for 2 hours, the crystalline material was collected by filtration and air-dried. The crude product was stirred in 50 ml of water for 10 minutes, filtered, and recrystallized from CH_2Cl_2 - hexane to yield **7**: mp 181~184°d (3.3 g, 65.5%). NMR ($CDCl_3$): δ 0.12 (s, 9H), 0.36 (s, 9H), 3.65 (s, 2H), 3.79 (s, 3H), 4.3 (s, 2H), 4.91 (d, 1H, J=5 Hz), 5.01 (s, 1H), 5.70 (dd, 1H, J=5 and 10 Hz), 7.3 (s, 5H), and 7.58 ppm (d, 1H, J=10 Hz). MS: M^+ 606, 591, 179 (base).

Anal. Calc'd for $C_{24}H_{34}N_6O_5S_2Si_2$: C, 47.55; H, 5.65; N, 13.87; S, 10.58.
Found : C, 47.73; H, 5.40; N, 14.02; S, 10.86.

A small sample of **7** was recrystallized from EtOAc for comparison with the material prepared by Method B and was found to possess the same X-ray powder pattern.

[B.] A mixture of **3a** (8 g, 24.4 mmol) and MSA (12.8 g, 97.6 mmol) was stirred in 100 ml of EtOAc until all of the reactants dissolved. An EtOAc solution (10 ml) of **4** (4.77 g, 26.8 mmol) was added dropwise to the stirred solution. The reaction mixture was swept with dry nitrogen, and the release of CO_2 was confirmed by use of a $Ba(OH)_2$ trap. After the addition of **4** was completed, stirring was continued for 2 hours, during which time a white crystalline precipitate formed which was collected by filtration, washed with water, and dried. Crystallization from CH_2Cl_2 - hexane yielded **7** which was indistinguishable from that prepared by Method A by NMR and X-ray powder diffraction.

7-D-(−)-Mandelamido-3-[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid (**1**)

[A.] 2-Propanol Solvate

An EtOH solution (5 ml) of **7** (1 g, 1.65 mmol) was heated for 10 minutes, then diluted with 25 ml of isopropyl alcohol and allowed to crystallize. Filtration yielded 0.45 g (52% yield) as a white crystalline solid. The NMR spectrum of **1** prepared in this manner was consistent with the isopropanol solvate of cefamandole, as was the X-ray powder pattern.

[B.] Pentahydrate

A mixture of **7** (2 g, 3.3 mmol), EtOH (50 ml), and water (4 ml) was heated for 10 minutes, then diluted with 100 ml of water. After chilling, the crystalline pentahydrate was collected by filtration (1.6 g, 88% yield). The X-ray powder pattern was identical to that of authentic cefamandole pentahydrate.

References

1) WICK, W. E. & D. R. PRESTON: Biological properties of three 3-heterocyclic-thiomethyl cephalosporin antibiotics. Antimicr. Agents & Chemoth. 1: 221~234, 1972
2) HALL, W. H.; D. N. GERDING & E. A. SCHIERL: Antibacterial activity of cefamandole, eight other cephalosporins, cefoxitin, and ampicillin. Curr. Ther. Res., Clin. Exp. 21: 374~389, 1977
3) MOELLERING, R. C.: Symposium on cefamandole. J. Infect. Dis. Suppl. 137: S1~S194, 1978
4) INDELICATO, J. M.; W. L. WILHAM & B. J. CERIMELE: Conversion of cefamandole nafate to cefamandole sodium. J. Pharm. Sci. 65: 1175~1178, 1976

5) GREENE, J. M.: Process for preparing 7-(α-hydroxy-α-phenyl) acetamido-3-[[(1-methyl-1H-tetrazol-5-yl) thio]methyl]-3-cephem-4-carboxylic acid and derivatives thereof. U.S. 3,840,531, 1974
6) RYAN, C. W.: 3,7-(Ring-substituted) cephalosporin compounds. U.S. 3,641,021, 1972
7) GLOMBITZA, K.: Acylierung der 6-Aminopenicillinsäure in wasserfreiem Medium. JustusLiebig's Ann. Chem. 673: 166~170, 1964
8) Personal Communication from K. S. YANG, Lilly Research Laboratories, Indianapolis, IN, U.S.A.
9) HILS, J. & K. RÜHLMANN: Die Umsetzung von Aminosäure mit Trimethylchlorsilan. II. Darstellung and Eigenschaften der Aminosäure-Silylester Hydrochloride. Chem. Ber. 100: 1638~1645, 1967
10) HURST, D. T. & A. G. MCINNES: The alcoholysis of trialkylalkoxysilanes. II. The preparation and chemistry of methyl 2,3,4-tri-O-trimethylsilyl-α-D-glucopyranoside. Canad. J. Chem. 43: 2004~2011, 1965
11) COREY, E. J. & A. VENKATESWARLU: Protection of hydroxyl groups as *tert*-butyldimethylsilyl derivatives. J. Amer. Chem. Soc. 94: 6190~6191, 1972