

Communications to the Editor

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A NEW METHOD FOR THE SYNTHESIS OF 7 α -METHOXYCEPHALOSPORINS

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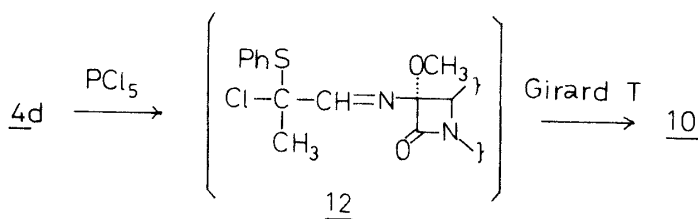
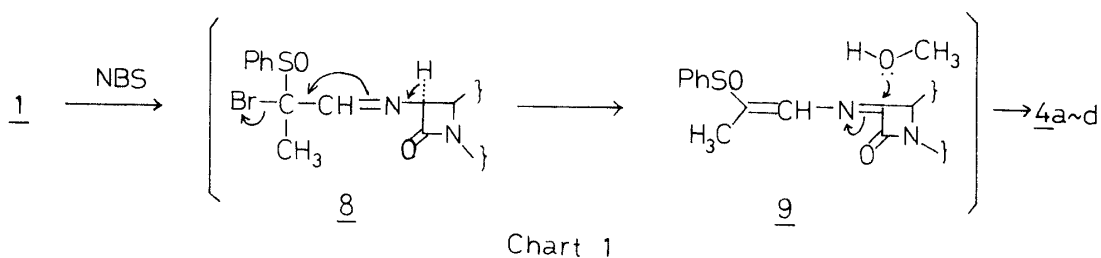
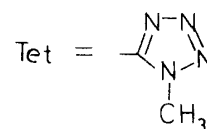
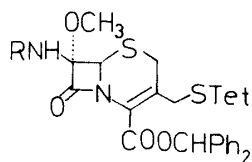
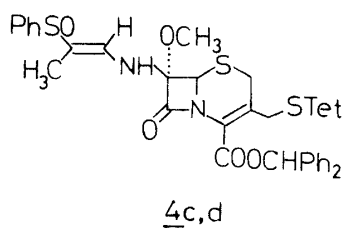
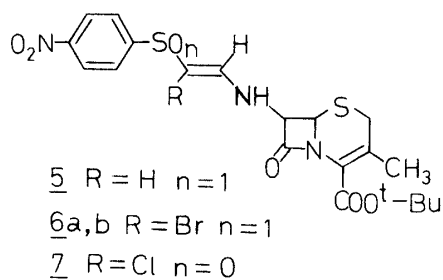
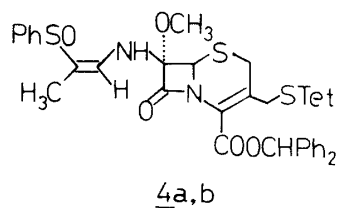
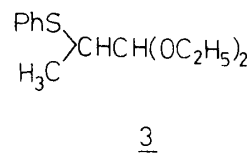
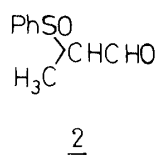
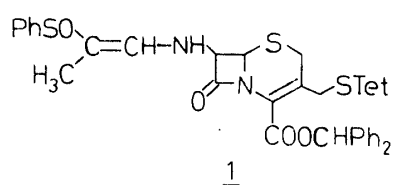
Bromination of the 7 β -benzenesulfinylpropenylaminocephalosporin (1) with NBS followed by treatment with methanol and sodium borate yielded the 7 α -methoxylated cephalosporins (4a~d). Removal of the side chain of the 7 β -amino group of 4d was achieved by treating it successively with PCl₅ and Girard T.

KEYWORDS ————— cephalosporin; 7 α -methoxycephalosporin; methoxylation; 7 β -sulfinylpropenylaminocephalosporin; 7 β -sulfinyl-enaminocephalosporin

Since the discovery of cephamycins in 1971,¹⁾ 7 α -methoxycephalosporins have been recognized as important β -lactam antibiotics which are particularly effective against gram-negative bacteria. Several methods have been developed²⁾ to introduce a methoxy group at the 7 α -position of cephalosporins. We wish to report a new methoxylation using 2-benzenesulfinyl-1-propenyl group as a reactive side chain of the 7 β -amino group of cephalosporins.

7 β -(2-Benzenesulfinyl-1-propenyl)aminocephalosporin ester (1) was prepared in 80% yield by condensation with 2-benzenesulfinylpropionaldehyde (2). The aldehyde (2) was synthesized from 2-benzenesulfinylpropionaldehyde diethylacetal (2)³⁾ by acid hydrolysis (c.HCl-CH₃CN = 1 : 2, 20 min.) and successive oxidation (m-CPBA, CH₂Cl₂, 20 min.). After 1 was brominated with 1 equiv. of NBS (-15°C, CH₂Cl₂, 25 min.), the reaction mixture was treated with methanol containing 1.5 equiv. of sodium borate⁴⁾ (room temp., 1 h) to introduce the methoxy group. Four isomeric 7 α -methoxylated compounds (4a~d)⁵⁾ with different R_f values on a silica gel TLC (Ph-CH₃ : AcOEt = 1 : 2) were obtained and were separated by silica gel column chromatography. As the products (4a~d) had the same M⁺ + 1 peak in FD-Mass spectra, and as their PMR spectra revealed an intact 7-methoxycephem nucleus, they were assumed to be two pairs of diastereomers originating from the double bond and sulfoxide. According to the report of Mikolajczyk et al.,⁶⁾ 4a and 4b, whose chemical shifts of the olefinic protons were higher than those of 4c and 4d, were assigned to the Z-configuration, and 4c and 4d to the E-configuration. But the stereochemistry of sulfoxide was not determined.

On the other hand, treatment of 5 with 1 equiv. of NBS afforded the brominated enamines (6a,b)⁷⁾ as epimers of sulfoxide, probably through bromination at the β -position of the enamine (5), followed by deprotonation from the nitrogen atom and isomerization. Thus, bromination of 1 was considered to give 8 analogously but in this case, since the absence of a proton on the brominated carbon atom made a



similar isomerization impossible, the following 1,4-dehydrobromination led to the intermediate (9) to which methanol was added to give 4a and as illustrated in Chart 1.

To remove the sulfinylpropenyl group from 4d, several attempts by the usual methods^{2),8),10)} were unsuccessful, probably because the presence of the sulfoxide group stabilized the enamine structure. Finally, we removed the sulfinylpropenyl group of 4d by treating with PCl_5 (-80°C , CH_2Cl_2 , DMA (N,N-dimethylaniline), 15 min.) and Girard T⁹⁾ (room temp., 1 h) to obtain the known amino ester¹⁰⁾ (10). The sulfinyl enamine (5), on similar treatment with PCl_5 (-80°C , CH_2Cl_2 , DMA, 20 min.), was converted to the chlorinated sulfide (7)¹¹⁾ which should be the product of a Pummerer-type reaction.^{12),13)} Analogously, formation of the intermediate (12) in the course of reaction from 4d to 10 was suggested as shown in Chart 2.

The amino ester (10) was acylated (BrCH_2COBr , DMA, -30°C , 30 min., AcOEt) to afford the amide (11) (50% from 4d) which is an intermediate for synthesizing clinically useful 7 α -methoxycephalosporins¹⁴⁾.

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- 5) Rf values: 4a, 0.64; 4b, 0.58; 4c, 0.41; 4d, 0.30. Yields: 4a, 4.4%; 4b, 5.3%; 4c, 35.5%; 4d, 34.7%. PMR(CDCl_3 , δ): 4a, 1.63(3H, d, $J=1.2\text{Hz}$, CH_3), 3.48(3H, s, OCH₃), 4.89(1H, s, C₆-H), 6.61(1H, q, $J=12\text{Hz}, 1.2\text{Hz}$, =CHNH); 4b, 1.63(3H, d, $J=1.2\text{Hz}$, CH_3), 3.43(3H, s, OCH₃), 4.89(1H, s, C₆-H), 6.61(1H, q, $J=12\text{Hz}, 1.2\text{Hz}$, =CHNH); 4c, 1.51(3H, d, $J=1.1\text{Hz}$, CH_3), 3.54(3H, s, OCH₃), 4.94(1H, s, C₆-H), 7.05(1H, q, $J=14\text{Hz}, 1.1\text{Hz}$, =CHNH); 4d, 1.52(3H, d, $J=1.2\text{Hz}$, CH_3), 3.50(3H, s, OCH₃), 4.94(1H, s, C₆-H), 7.05(1H, q, $J=12\text{Hz}, 1.2\text{Hz}$, =CHNH). IR(KBr , cm^{-1} (C=O): 4a, 1775; 4b, 1775; 4c, 1780; 4d, 1775. $[\alpha]_D^{25}$: 4a, -102° ($c=0.2$, CHCl_3); 4b, -22.1° ($c=0.14$, CHCl_3); 4c, -146.4° ($c=0.5$, CHCl_3); 4d, -29° ($c=0.2$, CHCl_3).
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- 7) 74% yield. PMR(CDCl_3 , δ): 6a, 7.53(1H, d, $J=12\text{Hz}$, =CHNH), 7.74(2H, d, $J=9\text{Hz}$, arom. H), 8.34(2H, d, $J=9\text{Hz}$, arom. H); 6b, 7.50(1H, d, $J=12.2\text{Hz}$, =CHNH), 7.75(2H, d, $J=9\text{Hz}$, arom. H), 8.35(2H, d, $J=9\text{Hz}$, arom. H).
- 8) The acid hydrolysis could not be adopted to obtain 7 β -amino-7 α -methoxycephalosporins because of its acid lability.
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- 11) 61% yield. FD-Mass $M^+ + 1 = 493$. PMR(CDCl_3 , δ): 6.84(1H, d, $J=12\text{Hz}$, =CHNH), 7.35(2H, d, $J=9\text{Hz}$, arom. H), 8.15(2H, d, $J=9\text{Hz}$, arom. H).
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- 13) Ishimaru et al. (M. Wakisaka, M. Hatanaka, H. Nitta, M. Hatamura, and T. Ishimaru, *Synthesis*, **1980**, 67) reported a reaction of this type in which dibenzyl sulfoxide was treated with PCl_5 in the presence of 1-morpholino-1-cyclohexene to give dibenzyl sulfide and 1-morpholino-6-chloro-1-cyclohexene. In the present case, we think that a similar type of reaction occurred intramolecularly to form 12.
- 14) a) See ref. 10). b) 7 β -(((2(R)-2-Amino-2-carboxyethyl)thio)acetamido)-7 α -methoxy-3-(((1-methyl-1H-tetrazol-5-yl)thio)methyl)-3-cephem-4-carboxylic acid (MT-141): T. Watanabe, K. Kawarajo, T. Tsuruoka, Y. Kazuno, and T. Niida, the 20 th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, U. S. A., Sept. 1980, Abstracts 161.

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