Tetrahedron Letters No. 34, pp 2947 - 2950, 1977. Pergamon Press. Printed in Great Britain.

A SYNTHESIS OF 7-METHOXYCEPHALOSPORIN AND ITS NOVEL REARRANGEMENT

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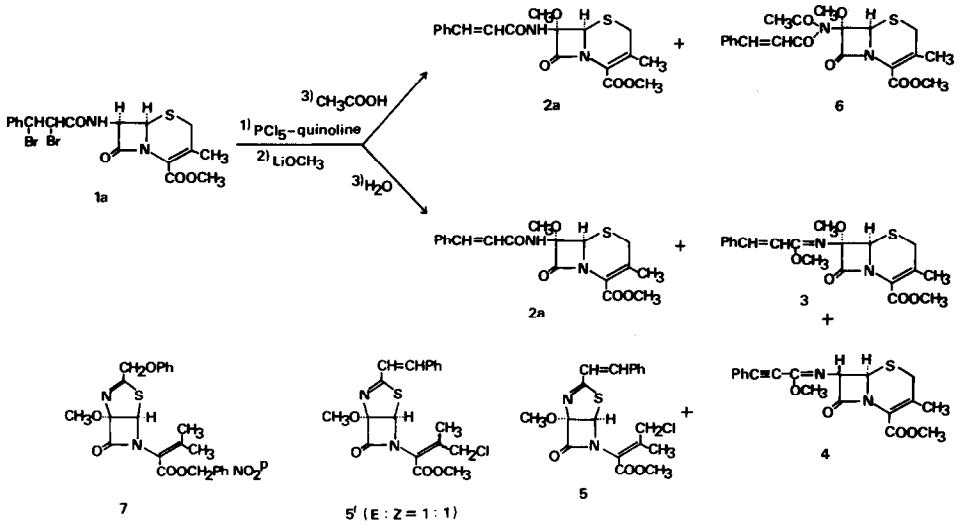
(Received in Japan 6 June 1977; received in UK for publication 5 July 1977)

Recently much effort has been directed towards the synthesis of 7-methoxycephalosporins because of the finding of the cephamycin group and their enhanced activity towards gram negative bacteria[1,2,3]. We also have studied and reported[4] some novel reactions for introducing a methoxy group at C_7 position of cephalosporins. Now we wish to report a modified C_7-methoxylation and a novel rearrangement of the resulting 7-methoxycephalosporin derivative.

7β-(3-Phenyl-2,3-dibromopropionyl)amino-3-methyl-3-cephem-4-carboxylic acid methyl ester (1a) was converted to the corresponding imino chloride with PCl_5-quinoline in chloroform, and subsequently reacted with an excess amount of a methanolic solution of lithium methoxide at -70° for 20 min. After quenching with water and following the usual work up, 7α-methoxy-7β-cinnamoylamino-3-methyl-3-cephem-4-carboxylic acid methyl ester (2a, 68.6%), 7α-methoxy-imino ether (3, 2.6%), 7-unsubstituted imino ether* (4, 3.7%) and a rearranged thiazoline derivative (5, 3.8%) were obtained. 2a: ir ν_{max}(nujol) 3300, 1775, 1730, 1675, 1630 cm^{-1}; nmr δ ppm($CDCl_3$) 2.10(3H, s), 3.22(2H, s), 3.55(3H, s), 3.77(3H, s), 5.12(1H, s), 6.70(1H, d, J=16 Hz), 7.2-8.3 (5H), 7.7(1H, d, J=16 Hz). 3: ir ν_{max}(liquid) 1770, 1730, 1645, 1605, 1597 cm^{-1}; nmr δ ppm ($CDCl_3$) 2.97(3H, s), 3.00 and 3.37(2H, AB-q, J=18 Hz), 3.36(3H, s), 3.77(6H, s), 4.92(1H, s), 7.03(1H, d, J=16 Hz), 7.1-7.5(6H). 4: ir ν_{max}($CHCl_3$) 2225, 1775, 1730, 1625 cm^{-1}; nmr δ ppm ($CDCl_3$) 2.09(3H, s), 3.20 and 3.48(2H, AB-q, J=18 Hz), 3.83(3H, s), 3.85(3H, s), 4.69(1H, d, J=2 Hz), 4.99(1H, d, J=2 Hz), 7.25-7.65(5H). 5: ir ν_{max}(liquid) 1780, 1730, 1630 cm^{-1}; nmr δ ppm($CDCl_3$) 2.20(3H, s), 3.50(3H, s), 3.67(3H, s), 3.85(2H, s), 5.72(1H, s), 7.00(1H, d, J=16 Hz), 7.17(1H, d, J=16Hz), 7.30(5H, s).

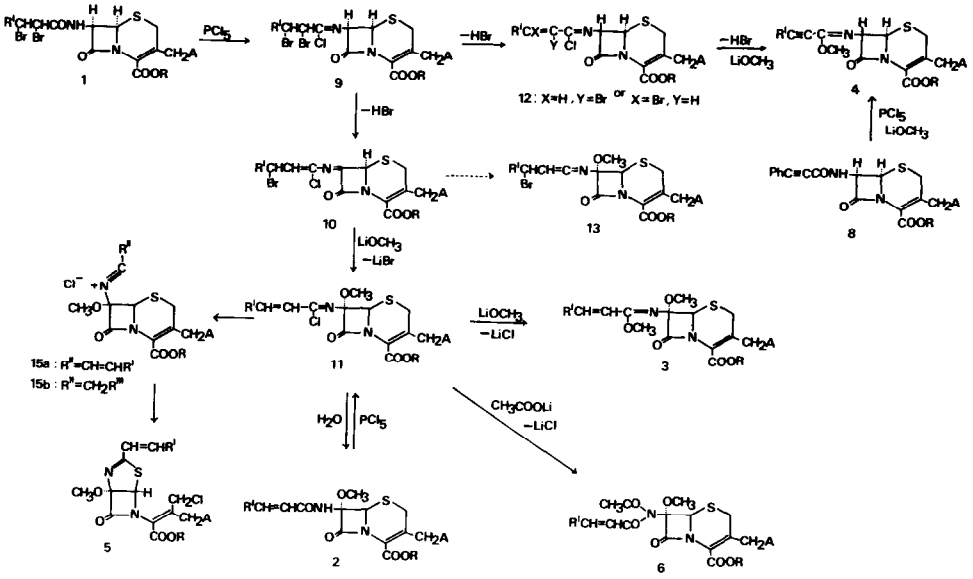
On the other hand quenching of the above reaction with acetic acid in place of water, in addition to 2a(28.1%), 7α-methoxy-7β-(N-cinnamoyl-N-acetyl)amino-3-methyl-3-cephem-4-carboxylic acid methyl ester(6) was obtained in 41.4% yield. 6: ir ν_{max}(liquid) 1780, 1725, 1700, 1620 cm^{-1}; nmr δ ppm($CDCl_3$) 2.24(3H, s), 3.36(3H, s), 2.97 and 3.54(2H, AB-q, J=16 Hz), 3.67(3H, s), 3.78(3H, s), 5.06(1H, s), 6.82(1H, d, J=16 Hz), 7.3-7.6(5H), 7.75(1H, d, J=16 Hz).



The structure of 4 was confirmed by an independent synthesis from 7β-phenylpropargylamido-3-methyl-3-cephem-4-carboxylic acid methyl ester(8) on treatment successively with PCl_5 and lithium methoxide**. The structure of the thiazoline derivative (5) was ascertained by comparing its nmr spectrum with that of 7[3g]. When 5 was treated with a base, such as triethylamine or lithium methoxide, the E-Z isomeric mixture (5', E:Z=1:1) was afforded, and the nmr spectrum of the isomer 5', especially the chemical shifts of CH_3 of the side chain (δ 1.80 and 2.20 ppm), suggested the configuration of the side chain of 5 as shown in the scheme.

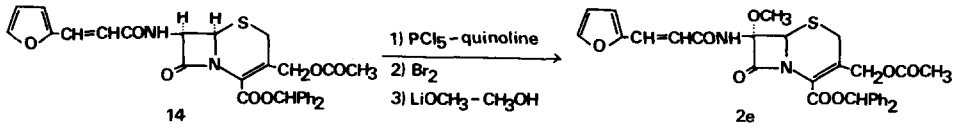
When 2a was treated with PCl_5-quinoline at room temperature to yield 7α-methoxy-imino chloride (11) and followed by treatment with lithium methoxide, the imino ether (3), thiazoline (5) and starting amide (2a) were obtained after the usual work up. If the imino chloride (11) was treated with lithium acetate in place of lithium methoxide, a tertiary amide (6) was obtained in addition to 2a and 5. However the imino chloride (11) gave the thiazoline (5, 27%) and the starting amide (2a, 70%) after usual work up with a phosphate buffer. From these experiments the mechanism of this methoxylation reaction was presumed as is shown in next page.

Our reported methoxylation reaction[4], suggests that the Michael addition of methoxyl group to exoimine (10) would give a 7-methoxyketenimine (13), but in this case the reaction occurred at 1,5-position to give imino chloride (11) by elimination of labile bromide which attached to an allylic C-atom. The resulting imino chloride was very reactive affording the amide (2a) with water, imino ether (3) with lithium methoxide, tertiary amide (6) with lithium acetate and thiazoline (5) by rearrangement.



Analogous methoxylation reaction was achieved successfully using 1b (R'=PhS-, A=OAc, R=$CHPh_2$), 1c (R'=2-thienyl, A=H, R=CH_3) and 1d (R'=2-thienyl, A=OAc, R=$CHPh_2$) to give the corresponding 2b, 2c and 2d in 25%, 57% and 45% yields respectively.

When the starting dibromoamide (1) was difficult to synthesize, another modified methoxylation was applied. 7β-Furylacrylamide-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (14) was converted to an imino chloride by PCl_5-quinoline, and reacted with a slight excess amount of bromine at -20° to afford dibromoimino chloride (9b, R'=2-furyl, A=OAc, R=$CHPh_2$). Successive treatment with lithium methoxide and following usual work up gave 7α-methoxy-7β-furylacrylamido-3-acetoxymethyl-3-cephem-4-carboxylic acid benzhydryl ester (2e) in 20% yield.



Although the rearrangement of a penicillin sulfoxide to a thiazoline derivative with trimethylphosphite is well known[5], such a rearrangement of a cephalosporin has not been reported. Recently Spitzer et al[6] observed such a rearrangement only in 6-fluoropenicillin imino chloride but not in 7-fluorocephalosporin imino chloride. They mentioned in their

report that in the rearrangement of the penicillin imino chloride to the thiazoline derivative, the inductive effect of C_6-fluorine and the angle between the two rings of penicillin play an important part. In our case it is very interesting that such a rearrangement occurred in the compound having a methoxy group and an even larger angle betweeh the two rings. We could not find any such rearrangement in the imino chloride prepared from 7α-methoxy-7β-substituted-acetamido cephalosporins which have at least one hydrogen atom attached to the sp^3-carbon located at the α-position of the amide. In such cases the intermediate iminium iron (15b) would be easily quenched to form a ketenimine. For these rearrangements at least 2 factors would be essential; firstly the absence of hydrogen at the 7α-position of the β-lactam, and secondly the absence of a hydrogen at the sp^3-carbon adjacent to the amide.

Acknowledgements. We are very grateful to Dr. K. Arima, the director of our research laboratories, Dr. G. Sunagawa, the former director, and Dr. Y. Kishida, the director of chemical research for their encouragement throughout this work.

References and Notes

1) (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, J. Amer.Chem. Soc., 93, 2308 (1971); (b) E. O. Stapley, M. Jackson, S. Hernandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff, and D. Hendlin, Antimicrob. Ag. Chemother., 2, 122 (1972); (c) T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, and F. J. Wolf, ibid., 2, 132 (1972); (d) P. P. K. Ho, R. D. Towner, J. M. Indelicato, W. J. Wilham, W. A. Spitzer, and G. A. Koppel, J. Antibiotics, 26, 313 (1973).

2) (a) S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, J. Amer. Chem. Soc., 94, 1410 (1972); (b) W. H. W. Lunn, R. W. Burchfield, T. K. Elzey, and E. V. Mason, Tetrahedron Lett., 1307 (1974).

3) (a) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, J. Amer. Chem. Soc., 94, 1408 (1972); (b) W. A. Spitzer and T. Goodson, Tetrahedron Lett., 273 (1973); (c) W. A. Slusarchyk, H. E. Applegate, D. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, J. Org. Chem., 38, 943 (1973); (d) H. E. Applegate, J. E. Dolfini, M. S. Puar, W. A. Slusarchyk, B, Toeplitz, and J. Z. Gougoutas, ibid., 39, 2794 (1974); (e) T. Jen, J. Frazee, and J. R. E. Hoover, ibid., 38, 2857 (1973); (f) L. D. Cama and B. G. Christensen, Tetrahedron Lett., 3505 (1973); (g) J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, J. Amer. Chem. Soc., 95, 2401 (1973); (h) G. A. Koppel and R. E. Koehler, ibid., 95, 2403 (1973); (i) R. A. Firestone and B. G. Christensen, J. Org. Chem., 38, 1436 (1973); (j) W. H. W. Lunn and E. V. Mason, Tetrahedron Lett., 1311 (1974); (k) P. H. Bently and J. P. Clayton, Chem. Comm., 278 (1974); (l) H. Yanagisawa, M. Fukushima, A. Ando, and H. Nakao, Tetrahedron Lett., 2705 (1975).

4) (a) Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, Tetrahedron Lett., 1307 (1976); (b) T. Saito, Y. Sugimura, Y. Iwano, K. Iino, and T. Hiraoka, Chem. Comm., 516 (1976); (c) Y. Sugimura, K. Iino, Y. Iwano, T. Saito, and T. Hiraoka, Chem. Pharm. Bull., 25, 369 (1977).

5) R. D. G. Cooper and F. L. Jose, J. Amer. Chem. Soc., 92, 2575 (1970).

6) W. A. Spitzer, T. Goodson, Jr., M. O. Chaney, and N. D. Jones, Tetrahedron Lett., 4311 (1974).

* A mixture of 6α,7α-(cis, 30%) and 6α,7β-(trans. 70%) hydrogen derivative.

** The ratio of cis/trans was just same as that of compound yielded from 1a.