Tetrahedron Letters No. 16, pp 1307 - 1310, 1976. Pergamon Press. Printed in Great Britain.

A NOVEL SYNTHESIS OF 7-METHOXYCEPHALOSPORINS AND 6-METHOXYPENICILLINS

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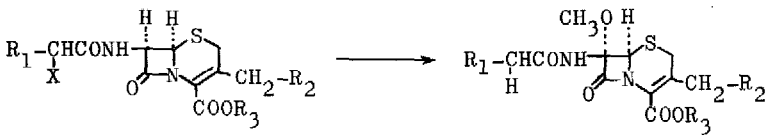
(Received in Japan 21 February 1976; received in UK for publication 11 March 1976)

Recently 7-methoxycephalosporin compounds have attracted the attention of many chemists and pharmacologists because of the finding of the natural cephamycin group and their enhanced activity against gram-negative bacteria[1,2] and much effort has been directed toward the development of a method for the introduction of a methoxyl group at the 7-position of the cephalosporin skeleton. Almost all of the successful method[3] reported up to the present have involved some kind of oxidative process. We now wish to report a new method which comprises a novel elimination to form a 7-imino intermediate, followed by stereospecific addition of the methoxy functionality. Thus 7β-(α-halogenoacetamido)cephalosporins 1 were converted into 7α-methoxy-7β-acetamidocephalosporin derivatives 2 in high yields.

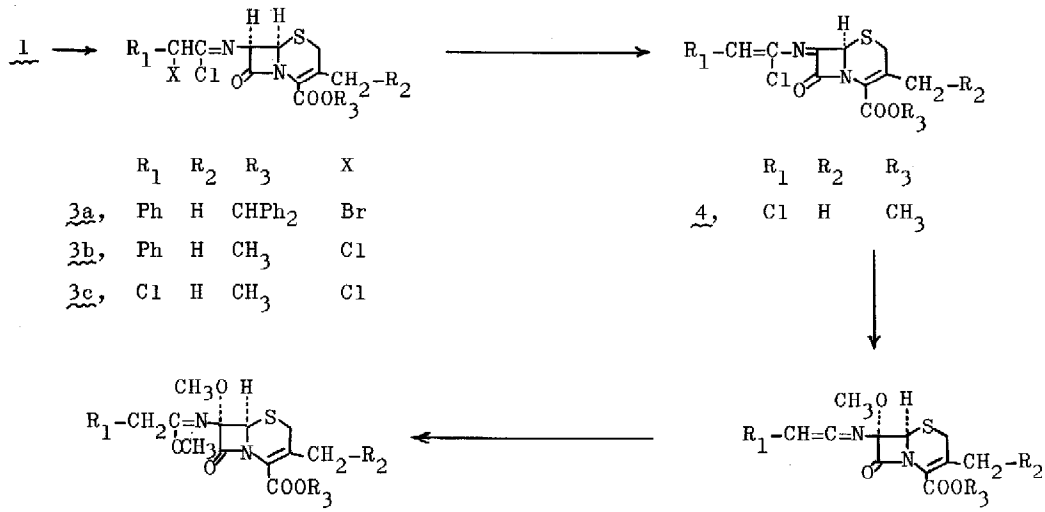


	R_1	R_2	R_3	X
1a,	Ph	H	$CHPh_2$	Br
1b,	Ph	H	$CHPh_2$	Cl
1c,	Ph	H	CH_3	Cl
1d,	Ph	H	$CHPh_2$	OH
1e,	Cl	H	CH_3	Cl
1f,	Cl	$OCOCH_3$	$CH_2COPh(Br\text{-}p)$	Cl
1g,	Cl	$OCOCH_3$	H	Cl

	R_1	R_2	R_3
2a,	Ph	H	H
2b,	Cl	H	CH_3
2c,	Cl	$OCOCH_3$	H

The key to this method is to produce an imine derivative 4 from an α-haloimino chloride 3 via 1,4-elimination with a base. The resulting imine 4 can be changed to methoxyketenimine 5 by the addition of the methoxide anion.

Treatment of the imino chloride 3a which was obtained from 7β-(2-phenyl-2-bromo)acetamido-3-methyl-3-cephem-4-carboxylic acid benzhydryl ester (1a) and PCl_5, with an excess of a methanolic solution of lithium methoxide in tetrahydrofuran (THF) at -78° for 20 min followed by quenching with acetic acid



	R_1	R_2	R_3	X
3a,	Ph	H	$CHPh_2$	Br
3b,	Ph	H	CH_3	Cl
3c,	Cl	H	CH_3	Cl

	R_1	R_2	R_3
4,	Cl	H	CH_3

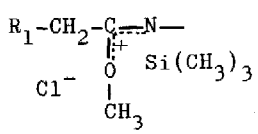
	R_1	R_2	R_3
5a,	Ph	H	$CHPh_2$
5b,	Ph	H	CH_3

	R_1	R_2	R_3
6a,	Ph	H	CH_3
6b,	Cl	H	CH_3
6c,	Cl	$OCOCH_3$	$CH_2COPh(Br\text{-}p)$
6d,	Cl	$OCOCH_3$	H

afforded 7β-phenylketenimino-7α-methoxy-3-methyl-3-cephem-4-carboxylic acid benzhydryl ester (5a) in 60% yield. This ketenimine 5a was purified by silica gel preparative TLC accompanied by slight decomposition: 5a, irν_{max}(liquid) 2000, 1780, 1730 cm^{-1}; nmr ($CDCl_3$)δ 2.20(3H, s), 2.93 and 3.13(2H, AB-q, J=18 Hz), 3.70(3H, s), 5.00(1H, s), 5.22(1H, s), 6.87(1H, s), 7.0-7.6(15H). Treatment of 5a with trifluoroacetic acid followed by quenching with water quantitatively afforded 7β-phenylacetamido-7α-methoxy-3-methyl-3-cephem-4-carboxylic acid (2a) which was identical with the compound obtained from Cephamycin C by a known method.[2] Analogous reactions starting from 1b and 1c gave 5a (60% yield) and 5b (95% yield), respectively. In the case of 1d, 5a was obtained by using excess PCl_5. When the temperature for treating the imino chloride 3b with lithium methoxide was -20° or the ketenimine 5b was treated with lithium methoxide at -20°, the imino ether 6a, was obtained in good yield: 6a, irν_{max}(liquid) 1770, 1730, 1645 cm^{-1}, nmr ($CDCl_3$)δ 2.07(3H, s), 3.07 and 3.49(2H, AB-q, J=18 Hz), 3.33(3H, s), 3.68(3H, s), 3.82(3H, s), 3.81 and 4.05(2H, AB-q, J=15 Hz), 4.97(1H, s), 7.25(5H, s). On the other hand in the case of the imino chloride 3c, which was formed from 7β-dichloroacetamido-3-methyl-3-cephem-4-carboxylic acid methyl ester (1e) as stable crystals of mp 105-108°, the imino ether 6b was

given in 80% yield by treatment with excess lithium methoxide at -78°: 6b, mp 138-139°; ir ν_{max}(nujol) 1770, 1713, 1668 cm^{-1}, nmr ($CDCl_3$) δ 2.07(3H, s), 3.07 and 3.35(2H, AB-q, J=18 Hz), 3.42(3H, s), 3.73(3H, s), 3.77(3H, s), 4.07 and 4.43 (2H, AB-q, J=12 Hz), 4.90(1H, s). Reaction of the imino chloride 3c with an organic base such as quinoline, triethylamine or DBN in THF at -60~0°, yielded the imine 4 as crystals of mp 156-159° in 80% isolated yield. This imine 4 was rather stable and could be purified by preparative silica gel TLC: 4, ir ν_{max} (nujol) 1770, 1722 cm^{-1}, nmr ($CDCl_3$) δ 2.20(3H, s), 3.35 and 3.53(2H, AB-q, J=18 Hz), 3.89(3H, s), 5.62(1H, s), 7.27(1H, s). The imine 4 was easily converted to the imino ether 6b by treatment with a methanol solution containing excess lithium methoxide at -78° in 85% isolated yield. Analogously, the imino ether 6c was obtained from the corresponding amide 1f in 40% yield.

The reactivity of the ketenimine was related to the substituent R_1, and when R_1 was phenyl or alkyl the ketenimine 5 was isolated. On the other hand the ketenimine with a substituent R_1 such as halogen, thienyl, PhS-, CH_3S- or CH_3SO_2- is sufficiently reactive to afford an imino ether 6 at -78° in THF-methanol in the presence of excess lithium methoxide. The resulting imino ether 6 should be convertible to the corresponding amide 2, however it would be rather difficult to induce this reaction in high yield without cleavage of the β-lactam ring, because imino ethers are generally converted to amides by alkaline hydrolysis[4] and under such conditions the β-lactam would also be hydrolyzed. This difficulty was overcome by finding a new reaction using an alkylhalosilane. The imino ether 6b was treated with an excess of trimethylchlorosilane and one equivalent of quinoline in chloroform at room temperature overnight. After working up with water 7β-chloroacetamido-7α-methoxy-3-methyl-3-cephem-4-carboxylic acid methyl ester (2b) was obtained in over 80% yield: 2b, mp 123-125°; ir ν_{max}(nujol) 3280, 1790, 1728, 1680 cm^{-1}, nmr ($CDCl_3$) δ 2.15(3H, s), 3.19(2H, s), 3.53(3H, s), 3.78(3H, s), 4.07(2H, s), 4.97(1H, s), 7.43(1H, broad s). This reaction might proceed via the intermediate 7 which would be transformed to 8 or 9, and the sililated amide 9 is considered more likely from the results of another experiment.[5]



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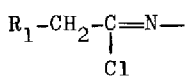

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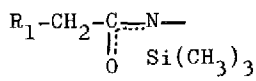

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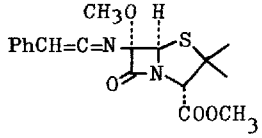
This conversion from an imino ether to an amide using an alkylhalosilane was applied to imino ethers having other substituents at R_1 such as PhS-, PhO, CH_3S-, CH_3SO_2- and thienyl to afford the corresponding amide 2 in good yields.

This methoxylation reaction was also applied to cephalosporin acid series.

In the case of 7β-dichloroacetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid (1g) the carboxylic acid was first protected as the silyl ester and then converted to imino chloride with PCl_5 at -50°. The resulting imino chloride was treated with a methanolic solution of excess lithium methoxide to afford the imino ether 6d. Without purification, this imino ether 6d was transformed to 2c with trimethylchlorosilane in 87% yield from 1g.

By the application of this methoxylation reaction to the penicillin series, 6α-methoxyketenimine 10 and 6α-methoxyimino ether 11 were obtained from the corresponding methyl 6β-(2-chloro-2-phenyl)acetamido and 6β-dichloroacetamido penicillanate, respectively.



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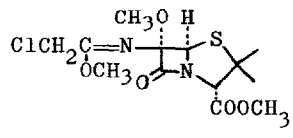

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Acknowledgements: We are very grateful to Dr. K. Arima, the director of our research laboratories, Dr. G. Sunagawa, the former director, and Dr. Y. Kishida, the vice director for their encouragement throughout this work.

References and Notes

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5. The results will be reported elsewhere.