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An alternative synthesis of clindamycin

KEITH BOWDEN and GRAHAM P. STEVENS

Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, Essex, UK, CO4 3SQ

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A novel synthesis of clindamycin from lincomycin using *N*-chlorosuccinimide and triphenylphosphine is reported. This results in high yields and avoids the use of tetrachloromethane employed in the current manufacturing process.

Keywords: clindamycin, *N*-chlorosuccinmide.

INTRODUCTION

Clindamycin [(2S-*trans*)methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4- propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-L-threo-α-D-galacto- octopyranoside] **1** is a semisynthetic antibacterial originally discovered by Upjohn in 1969.[1] The hydrochloride salt of clindamycin is used in the treatment of serious infections caused by Gram-positive organisms, *i.e., Staphylcocci*, *Streptococci* and *Pneumococci*, as well as having good activity against a wide range of anaerobic bacteria.[2] Clindamycin **1** can be prepared by chlorination of the related antibacterial, lincomycin **2**.[3] However, clindamycin has between four and eight times the antibacterial activity of lincomycin.[3]

Three methods for the synthesis of clindamycin from lincomycin have been reported by Birkenmeyer and Kagan.[3] The first involved the treatment of lincomycin hydrochloride with thionyl chloride in tetrachloromethane *via* intermediate cyclic sulfites. This involves inversion of configuration at C-7. The second employs triphenylphosphine dichloride in acetonitrile to convert lincomycin to clindamycin. This method is known to chlorinate alcohols with inversion of configuration.[4,5] The third involved the use of triphenylphosphine and tetrachloromethane which is a procedure known to chlorinate alcohols with inversion of configuration.[6,7] In 1986 an improved method for the preparation of clindamycin was described[8] in which the chlorination is achieved by the use of Vilsmeier-type reagents prepared from the reaction of amides, such as *N*-formylpiperidine and *N*-formylmorpholine, with phosgene or thionyl chloride. These reagents are known to chlorinate secondary alcohols with inversion of stereochemistry.[9]

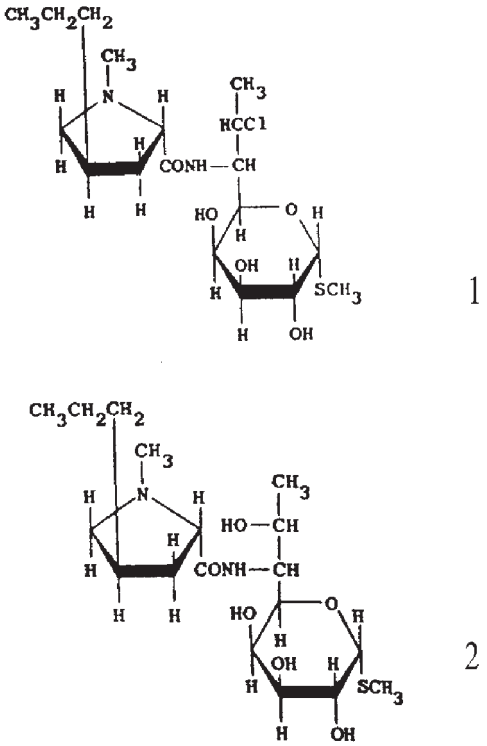

Fig. 1. Structures of clindomycin **1** and lincomycin **2**.

The method using triphenylphosphine and tetrachloromethane is the basis of the process that is in current use in the manufacture of clindamycin. Since the use of tetrachloromethane is restricted and is to be banned for such processes, an alternative reagent is required. Alternative processes have been evaluated and a viable method has been found.

DISCUSSION AND RESULTS

The chlorination of lincomycin and a protected lincomycin, the 3,4-isopropylidene ketal of lincomycin, was investigated. Firstly, a preliminary examination has been made of a series of potential chlorinating reagents. The most encouraging results, *i.e.,* good yields of clindamycin *alone*, were obtained using *N*-chlorosuccinimide (NCS) or anhydrous chloral and triphenylphosphine (PPh_3) with the protected lincomycin. No reaction was observed with bis(benzonitrile)palladium(II) chloride and with *N*,*N*-diethyltrichlorovinylamine. Decomposition and/or several products were given with thionyl chloride, phosphorus pentachloride and sulfuryl chloride without or with PPh_3, as well as with zinc chloride, with DEAD(diethyl azodicarboxylate) and PPh_3, and with tosyl chloride/LiCl. Secondly, the conditions of the chlorinations using NCS and PPh_3, regarding solvent, temperature, concentrations and time, were studied. No solvent showed any signifi-

cant advantage over tetrahydrofuran (THF) at the reflux temperature of this solvent. Typical optimised experiments are described below.

The mechanism of these reactions would appear to be chlorination with inversion of configuration resulting from the breakdown of triphenylphosphonium salt, *cf.* Ref. 10. Thus, the chlorotriphenylphosphonium salt, from NCS and PPh_3, is formed first and then reacts with alcohol to give the alkoxytriphenylphosphonium salt. The reaction is then completed by an S_N2 displacement on the latter salt by chloride anion.

EXPERIMENTAL

The structures of all compounds were confirmed by spectroscopy and microanalysis. ^1H and ^{13}C-NMR spectra were recorded at ambient in deuterated chloroform or dimethyl sulfoxide using a JEOL EX270 FT spectrometer with Me_4Si as internal standard. Mass spectra were recorded using an AEI MS 50 double focusing spectrometer.

Chlorination process

NCS (1.34 g, 0.01 mol) was dissolved in THF (60 ml) and the resulting solution added to a solution of PPh_3 (2.62 g, 0.01 mol) in THF (60 ml). To the resulting mixture was added a solution of the free base of lincomycin or protected lincomycin (0.005 mol) in THF (20 ml). The resulting mixture was stirred, heated at reflux temperature for 18 h and then concentrated to dryness under reduced pressure. The residue was dissolved in aqueous HCl (1 mol dm^{-3}) (150 ml) and dichloromethane (50 ml), before stirring vigorously for 12 h. The aqueous layer was separated, basified with aqueous NaOH (32 %) and extracted with dichloromethane (3 × 25 ml). The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude product. The latter was then examined/purified by TLC and HPLC (silica/methanol/chloroform). The yield of clindamycin and protected clindamycin was 84 and 80 %, respectively.

ИЗВОД

АЛТЕРНАТИВНА СИНТЕЗА КЛИНДАМИЦИНА

KEITH BOWDEN and GRAHAM P. STEVENS

Department of Bilogical and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, Essex, UK, CO4 3SQ

Приказана је нова синтеза клиндамицина полазећи од линкомицина коришћењем *N*-хлоросикцинимида и трифенилфосфина. Овим се добијају високи приноси и избегава коришћење тетрахлорметана као што је сада случај у процесима производње клиндамицина.

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REFERENCES

1. R. D. Birkenmeyer, U.S. Patent 3,435,025, March 25, 1969 (*C. A.* **71** (1969) 81696x)
2. J. E. F. Reynolds, Ed., *Martindale. The Extra Pharmacopoeia*, 29th Edn., The Pharmaceutical Press, London, 1989
3. R. D. Birkenmeyer, F. Kagan, *J. Med. Chem.* **13** (1970) 616
4. G. A. Wiley, R. L. Hershkowitz, R. B. Rein, B. C. Chung, *J. Am. Chem. Soc.* **86** (1964) 964
5. G. A. Wiley, B. J. Rein, R. L. Hershkowitz, *Tetrahedron Lett.* **36** (1964) 2509
6. J. B. Lee, I. M. Downie, *Tetrahedron* **23** (1967) 359

7. D. Brett, I. M. Downie, J. B. Lee, *J. Org. Chem.* **32** (1967) 855
8. R. D. Birkenmeyer, U. S. Patent 3,475,407, Oct 28, 1969 (*C. A.* **73** (1970) 25835w)
9. D. R. Hepburn, H. R. Hudson, *J. Chem. Soc. Perkin Trans. 1* (1976) 754
10. R. M. Magid, O. S. Fruchey, W. L. Johnson, T. G. Allen, *J. Org. Chem.* **44** (1979) 359; R. M. Magid, B. G. Talley, S. K. Souther, *J. Org. Chem.* **46** (1981) 824.