General Method for the Synthesis of β-Lactam Antibiotics Substituted α to the β-Lactam Carbonyl

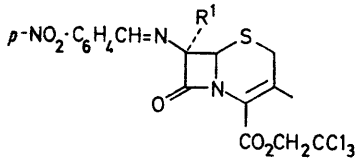
By W. A. SPITZER,* T. GOODSON, R. J. SMITHEY, and I. G. WRIGHT
(*The Lilly Research Laboratories, Indianapolis, Indiana* 46206)

Summary A general method for the synthesis of β-lactam antibiotics substituted α to the β-lactam carbonyl is demonstrated by the reaction of the appropriate Schiff base-stabilized anion with a variety of reactive halide reagents.

THE prediction of Strominger and Tipper that 6-methyl-penicillins and 7-methyl-cephalosporins should have enhanced antimicrobial activity,[1] coupled with the recent discovery that naturally occurring 7-methoxy-cephalosporins have unique antimicrobial properties,[2] has led to

interest in synthesizing penicillins and cephalosporins that are substituted α to the β-lactam carbonyl.[3] Recently, two groups have prepared 6-methylpenicillins and 7-methylcephalosporins by alkylation of a Schiff base-stabilized β-lactam anion with methyl iodide.[4] We have used a similar technique to synthesize these methyl compounds, and have found the same method generally applicable to the synthesis of other derivatives by treating the Schiff base anion with active halide reagents (alkyl halides, acyl halides, and α-halogeno carbonyl compounds).

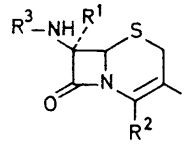
The synthesis of 7-carboxydeacetoxycephalosporin (IIc) illustrates a typical procedure. Schiff base (Ia) was prepared in quantitative yield by stirring the trichloroethyl ester of 7-ADCA with one equivalent of *p*-nitrobenzaldehyde in absolute ethanol at room temperature for 30 min. The Schiff base anion was generated by adding a 10 mmol THF solution of lithium di-isopropylamide† to a 10 mmol THF–DMF solution of (Ia) at −78°. After 5 min, 20 mmol of trichloroethyl chloroformate was added, and the reaction mixture was allowed to warm slowly to room temperature giving the acylated Schiff base (Ib) in 90% yield.‡



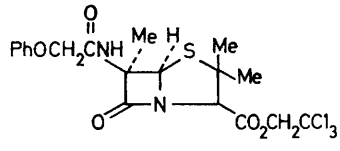
(I)

a; R^1 = H

b; R^1 = $CO_2CH_2CCl_3$



(II)



(III)

a; R^1,R^2 = $CO_2CH_2CCl_3$, R^3 = H

b; R^1,R^2 = $CO_2CH_2CCl_3$, R^3 = $COCH_2$

c; R^1,R^2 = CO_2H, R^3 = $COCH_2$

The acylated nucleus ester (IIa) was then generated by treatment of a THF–MeOH (4:1) solution of (Ib) with amino-oxyacetic acid hemihydrochloride. (IIa) was obtained in 34% yield when precipitated as the crystalline toluene-*p*-sulphonate salt; m.p. 180—182°.‡ The free amine was then treated with an acid chloride in CH_2Cl_2–pyridine at −45° to give the amide (IIb) in nearly quantitative yield.‡

Removal of both trichloroethyl ester blocking groups from (IIb) was easily effected with zinc and acetic acid in DMF to give the dicarboxylic acid (IIc) in good yield [δ ($CDCl_3$) 2·20 (s, 3H,–CH_3), 3·34 (s, 2H, –CH_2–), 3·93 (s, 2H, –CH_2), 5·50 (s, 1H, 6-H), 6·80—7·30 (m, 3H, thiophen)].‡

Similarly, other acyl halides have been used to give the corresponding 7-acyl-cephems. α-Halogenocarbonyl compounds such as phenacyl bromide and methyl α-bromoacetate and a variety of alkyl halides, particularly the more reactive bromides and iodides (such as benzyl and allyl), also react to give 7-substituted derivatives. The process is equally applicable to alkylation or acylation of the Schiff bases of 6-APA or 7-ACA esters, although in the 7-ACA system, care must be taken to avoid $\Delta^3 \rightarrow \Delta^2$ double bond isomerization.

In all cases, only one of the two possible stereoisomers at C-6 or C-7 was obtained. The α stereochemistry was established for (III) by the existence of a 17% nuclear Overhauser effect between the C-6 methyl group and the C-5 α hydrogen. The electrophilic attack on the Schiff base anion must be restricted by steric hindrance to the exposed α face of the β-lactam ring.[4b]

In certain cases in which the new substituent was large and electron withdrawing, acylation of the free amine was difficult. For example, when the substituent was benzoyl, acylation to give the corresponding amide could not be carried out under the usual acid chloride–base conditions without $\Delta^3 \rightarrow \Delta^2$ double bond isomerization. This problem was avoided by using propylene oxide as the HCl acceptor.[5]

All the new 7-substituted semisynthetic antibiotics were tested against a variety of micro-organisms. The new derivatives were all active, but less so than the unsubstituted parent compounds. Nevertheless, the broad general utility of the reaction scheme lends itself to the further investigation of β-lactam antibiotics with novel substituents.[6]

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† Other bases including sodium hydride and t-butyl-lithium may also be used.

‡ N.m.r., i.r., u.v., and mass spectra gave correct values.

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