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THE CHEMISTRY OF CEPHAMYCINS. V. THE REACTIONS OF THE CARBAMOYL GROUP

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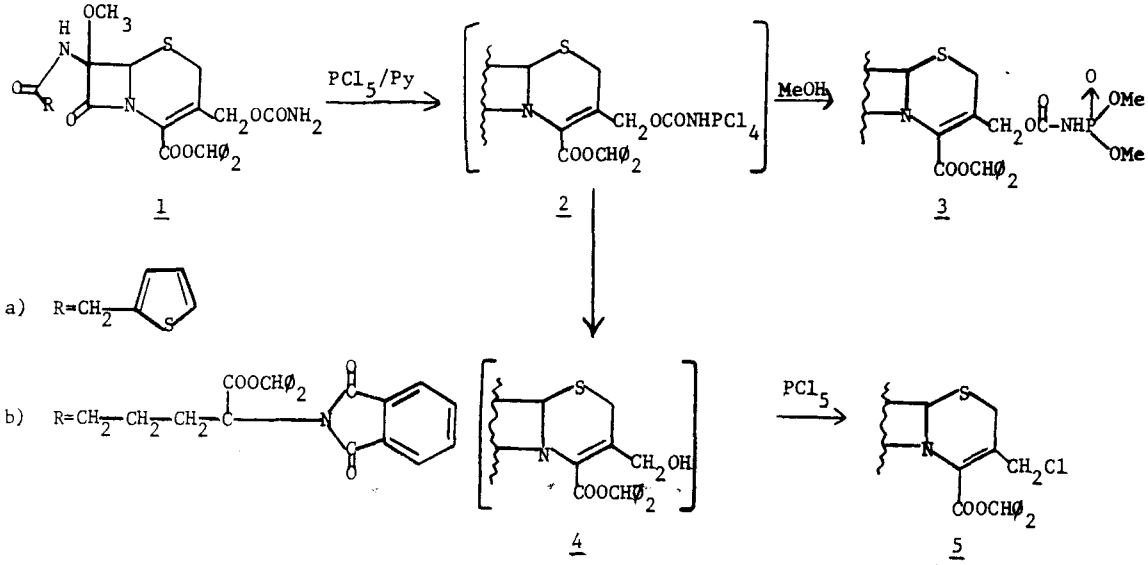
The chemistry of cephamycins has been the subject of recent communications from these laboratories[1,2]. Continuing our efforts to describe the reactivity of this system, we report on the reaction of Δ^3 carbamoyloxy function with electrophiles and nucleophiles.

Reaction with Electrophiles

In an earlier paper[1], we have shown that the 7-amido nitrogen of cephamycins (1a) can be selectively acylated with acid chlorides in the presence of a neutral acid scavenger, without involvement of the carbamoyloxy group. In contrast to this, here we report that PCl_5, $(Me_2NCHCl)Cl$ and $ClSO_2NCO$ attack the urethane nitrogen selectively.



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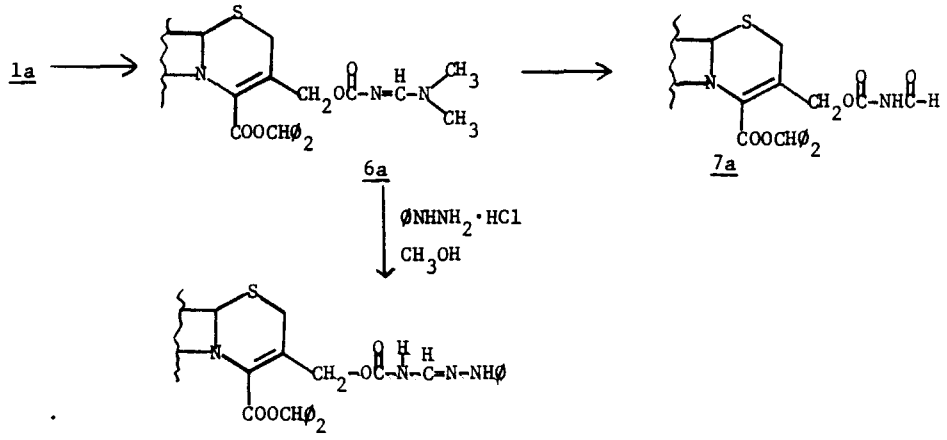
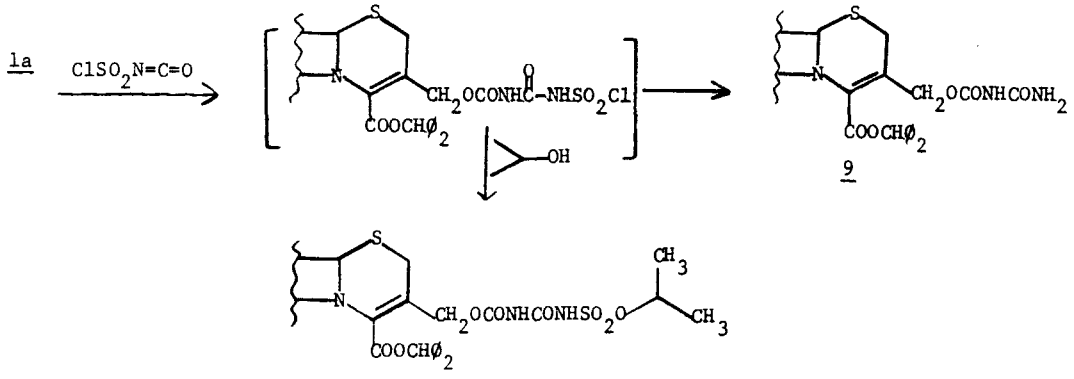
Thus, protected cephamycin C 1b reacted with PCl_5 and pyridine (in CH_2Cl_2 at 0° for 2 hrs), followed by methanol, to afford 3b[3] nmr[4] δ: 3.5 (s, C_7-OCH_3), 3.7 (d, P-OCH_3, $J_{P\text{-}OCH_3}$ = 7 Hz) 4.7 (br.s. CH_2OCO) 5.02 (s, C_6-H), in 25% isolated yield. A minor product (6% yield) was identified as the 10-chloro derivative 5b, nmr: δ 3.42 (s, C_7OCH_3), 4.32 (s, CH_2Cl), 5.03 (s, C_6-H). This formed presumably by the elimination of a phosphonyl isocyanate from 2b and further reaction of 4 with PCl_5.

Vilsmeyer reagent derived from DMF and $SOCl_2$ reacted smoothly with the carbamoyloxy function (in THF at 0° for 1 hr) to afford amidine 6a in nearly quantitative yield, nmr: δ 3.0 $(CH_3)_2N$, 3.6 $(CH_2$-CON), 5.0 $(CH_2$-OCO) and 5.05 (C_6-H). This reaction can be used for the reversible protection of the urethane group, since reaction with hydrazine dihydrochloride in methanol (r.t. 48 hr) yielded the starting 1a in high yield. The overall yield of 1a→6a→1a was about 75%.



Amidine 6a is a versatile intermediate which can be converted to formyl derivative 7a; nmr δ 8.8 (d, J = 8 Hz, $\overset{O}{C}$-H), by treatment with 4 equivalents of trifluoroacetic acid in THF for 4 hrs at room temperature. Furthermore, the dimethylamino group can be replaced with phenylhydrazine (CH_3OH, r.t. 4 hrs) to afford 8a. Another electrophilic reagent, chlorosulfonyl isocyanate, selectively attacked the carbamoyl nitrogen. The initial adduct was converted to allophanate 9a [nmr: δ 5.0 (q. J_{AB} = 10 Hz, CH_2-OCO) correct C, H, N and S] with KI in acetone at 0°, and to 10a [nmr δ 1.35 (d, J = 6 Hz $(CH_3)_2CHO$-) and 2.4 (d, J = 6 Hz, CH-O)] with isopropanol and collidine (0° for 30 min).



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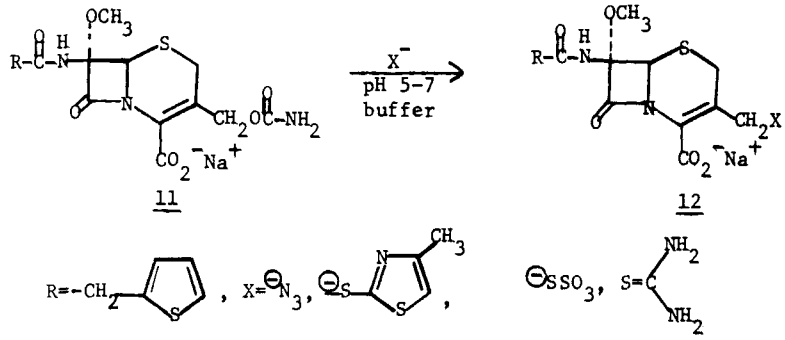
Reaction with Nucleophiles

Abraham, Newton and Hale[5] first reported the displacement of the acetoxy group in cephalosporin C. A study of this replacement by "soft" nucleophiles (e.g. $\ominus N_3$, $\ominus SR$, thiourea, etc.) was reported in an elegant paper by Cocker and co-workers[6], wherein strong evidence was presented for an SN_1 type displacement.

We have found that the C-10 carbamoyloxy group in cefoxitin 1a is also replaced in a related process. To our knowledge this is the first instance of alkyl oxygen cleavage in carbamate solvolysis. The method is useful for the preparation of various 10-substituted cephalosporins containing a 7α-methoxy group.



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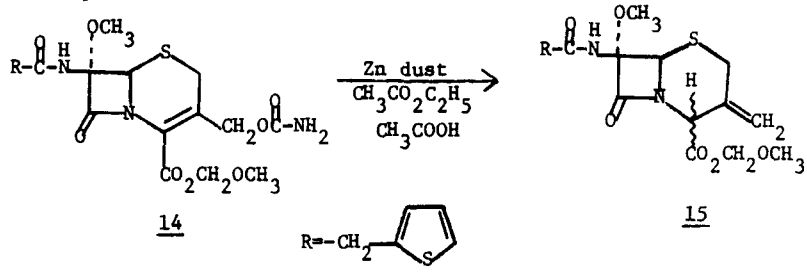
In general, the reaction is carried out by heating at 90° for eight minutes (or two days at 45°) a pH 5-7 aqueous solution (0.5M in $PO_4^{\equiv}$) of cefoxitin containing a ten-fold molar excess of nucleophile. The compounds (12) were purified by preparative thick layer chromatography. [X=N_3, ir ($CHCl_3$) 2120 (γN_3), 1780 ($\gamma C{=}O$), 1720 ($\gamma C{=}O$), 1690 ($\gamma C{=}O$) cm^{-1}; nmr ($CDCl_3$) δ 3.2-3.6 (s and m, OCH_3, $S\text{-}CH_2$) 3.9-4.4 (m, $C_{10}H_2$), 5.08 (s, C_6H). When X=-2—

mercapto-4-methylthiazole nmr $(CD_3)_2CO$ δ 2.3 (s, CH_3-thiazole ring), 3.4 (s, OCH_3), 4.2-4.7 (m, $C_{10}H_2$), 5.08 (s, C_6H). Mass spectrum (as methyl ester) M^+ 512.]

The yields are in the range of 20-30% because of the concommitant cleavage of the β-lactam.

The carbamoyloxy group was removed reductively, the product depending on conditions. The carbamoyloxy group of 11 was removed by hydrogenation over 5% Pd/C in aqueous solution at pH 7 producing the 3-methyl analog 12 (X=H)[7], whereas novel reaction of the carbamoyloxy group was observed when the cefoxitin methoxymethyl ester 14 was treated with zinc dust to give the exometnylene compound[8] 15 identified by its characteristic nmr spectrum [$(CDCl_3)$ δ 3.5 (s, OCH_3), 3.9 (s, $-CH_2\overset{O}{\overset{\|}{C}}-$), 5.2-5.6 (s and m, C_6H and $=CH_2$)] mass spectrum (M^+ 412) and its lack of UV adsorption at 270 nm.



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2. S. Karady, T. Y. Cheng, S. H. Pines and M. Sletzinger, Tet. Letters, 2625, 2629 (1974).
3. This finding is contrary to German Patent 235 1375, October 12, 1973, of E. Lilly Co., where imidoyl chloride was claimed without reaction of the urethano nitrogen.
4. Only diagnostic peaks are given. All spectra were in deuterochloroform.
5. C. N. Hale, G. G. Newton and E. P. Abraham, Biochem. J., 78, 403 (1961).
6. J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Kardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly and G. A. Somerfield, J. Chem. Soc., 5015 (1955).
7. The methyl compound was first prepared by Dr. S. Pines from these laboratories.
8. M. Ochiai, et al., Tet. Let., 2341-4 (1972).