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THE CHEMISTRY OF CEPHAMYCINS. III. REPLACEMENT OF THE CARBAMOYLOXY GROUP

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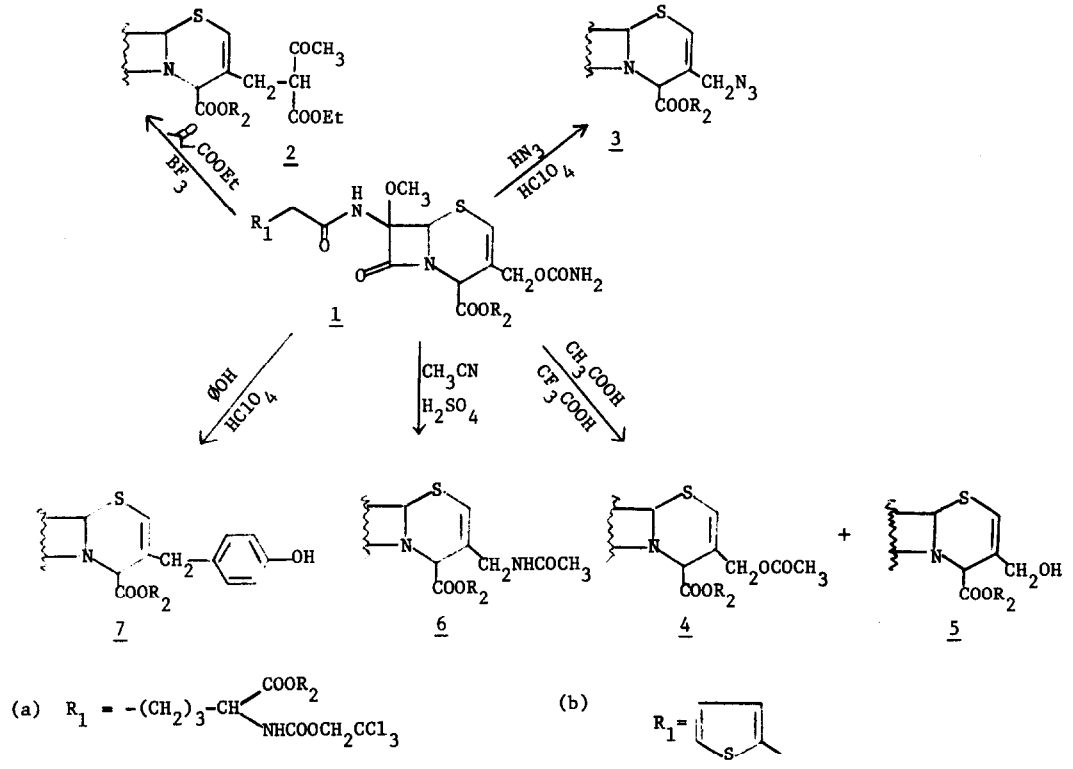
The preceding publication[1] described the cleavage of the C_{10}-O[2] bond of Δ^2 cephems with hydrohalic acids to form the corresponding 10-halo compounds. We now wish to show that this cleavage reaction is of a general nature; that is, the carbamoyloxy group of cephamycins can be replaced directly by a variety of nucleophiles.

When the conjugate acid of the nucleophile to be introduced is allowed to react with the Δ^2 cephem ester in the presence of a non-nucleophilic strong acid (or Lewis acid), cleavage occurs and the desired substituent is attached in one direct step. Generally, the reactions are conducted at 0° for a few hours with an excess of the two reagents. The progress of the cleavage can be followed by TLC. The versatility of this method is illustrated with the following examples [3] which are shown schematically on the next page.

Cephamycin derivative 1a[1] (R_2=CH_3) reacted with an excess of ethyl acetoacetate and BF_3-etherate in CH_2Cl_2 to afford compound 2a in 50% yield[3], NMR[4] ($CDCl_3$) δ1.25 (t, J=6 Hz, $COOCH_2\underline{CH_3}$), 2.28 (s, CH_3CO-), 2.75 (d, J=7 Hz, C_{10}-H_2), 4.12 (q, J=6 Hz, $COO\underline{CH_2}$-CH_3). The spectrum also indicated the presence of an enolized form in smaller concentration.

For the preparation of 10-azido derivative 3b, 1b (R_2=ϕ_2CH) was reacted with hydrazoic acid and 70% $HClO_4$ in CH_2Cl_2 and THF (17% yield). The product showed similar spectral characteristics to the azido derivative reported in the preceding paper[1]: $\nu_{max}^{CHCl_3}$ 2100 cm^{-1} (-N_3); NMR ($CDCl_3$) 3.88 (s, CH_2N_3).



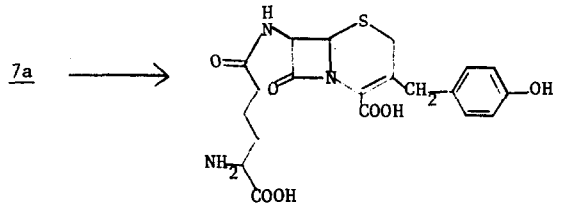
(a) $R_1 = -(CH_2)_3-CH(COOR_2)NHCOOCH_2CCl_3$ (b) $R_1=$

A mixture of trifluoroacetic acid and acetic acid was used to convert 1a ($R_2=CH_3$) to acetoxy derivative 4a (10% yield), NMR ($CDCl_3$) δ 2.5 (s, CH_3CO) and alcohol 5a [1] (80% yield). The formation of the latter compound was caused by adventitious water in the system. Acetylation (pyridine + acetic anhydride) converted 5a to 4a.

A Ritter type reaction of 1a ($R_2=CH_3$) in CH_2Cl_2 with acetonitrile and concentrated H_2SO_4 yielded 6a (30% yield), NMR ($CDCl_3$) δ 2.0 (s, CH_3CON), 4.0 (partially visible $C_{10}-H_2$).

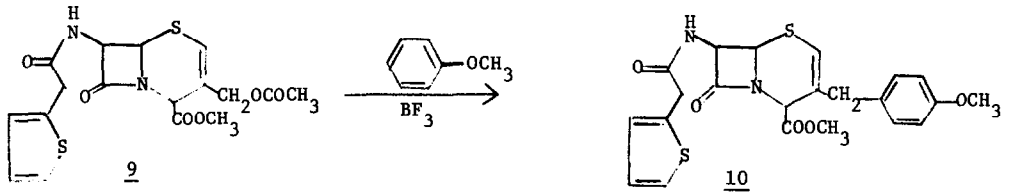
The reaction of 1a ($R=\emptyset_2CH$) with phenol and 75% $HClO_4$ in CH_2Cl_2 and THF gave p-hydroxyphenyl derivative 7a, NMR ($CDCl_3$) δ 3.3 (partially visible $C_{10}-H_2$), 6.85 (q, J_{AB}=10 Hz, aromatic protons) in 39% yield. The same reaction with BF_3-etherate produced the dicarboxylic acid corresponding to 7a in 43% yield.

Return to the biologically interesting Δ^3 series was accomplished by the usual oxidative-reductive isomerization method.[5] On such treatment, followed by the removal of the protecting groups, 7a was converted to 8; mp 185-190°(dec), UV $_{max}$ (pH 7 buffer) 2670 nm (ε 10.000), NMR (D_2O) δ 1.6-2.6 (m, O=C-$(CH_2)_3$), 3.10 (m, C_{10}-H_2), 3.5-3.6 (s and m, OCH_3 and S-CH_2), 5.08 (s, C_6-H), 7.0 (q, J_{AB}=8 Hz, aromatic protons).



7a 8

The acetoxy group of cephalosporins can be replaced with equal ease. When Δ^2-cephalothin ester 9 was treated with BF_3-etherate and anisol in methylene chloride, the p-methoxyphenyl derivative 10, NMR ($CDCl_3$) δ 3.45 (br.s, C_{10}-H_2), 6.8-7.3 (m, aromatic protons), was produced in about 25% yield.



9 10

References:

(1) S. Karady, T. Y. Cheng, S. H. Pines, and M. Sletzinger, Tetrahedron Lett.

(2) See footnote (3), reference 1.

(3) No attempt was made to optimize reaction conditions. The isolation of the products was usually done by preparative TLC.

(4) Only diagnostic spectral data are given. For physical data on cephalosporins and cephamycins, see 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); G. F. H. Green, J. E. Page and S. E. Staniforth, J. Chem. Soc., 1595 (1965).

(5) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright and E. M. Van Heyningen, J. Org. Chem., 35, 2430 (1970).