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The Chemistry of Cephamycins VI. Cleavage of the 7-Amido Group

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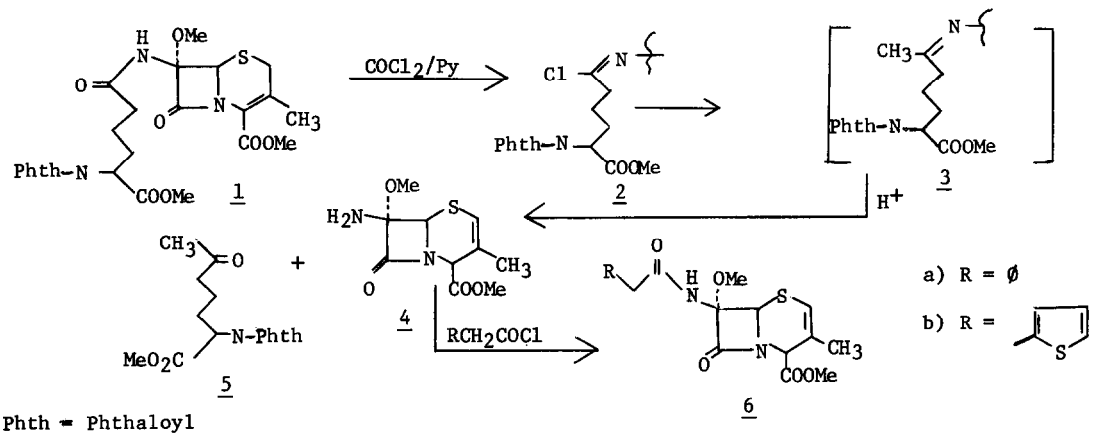
An important factor in the preparation of pharmacologically useful cephalosporins from readily available fermentation products is the exchange of the aminoadipoyl side chain with other acyl groups. Traditional transacylation methods utilize 7-aminocephalosporanic acid derivatives as a key intermediate[1] but in the case of the 7-α-methoxy series (the cephamycins) novel transacylations were developed aimed specifically at bypassing the acid labile 7-β-amino-7-α-methoxy intermediate.[2,3] Subsequently Lunn et al.[4] succeeded in effecting a cephamycin transacylation via a 7-aminomethoxy intermediate which was generated on acid catalyzed methanolysis of an imidoyl chloride. The product, however, was extensively epimerized at C-7. We wish to report on a method for transacylation of 3-methyl-cephamycins which proceeds via the 7-aminomethoxy intermediate but which does not result in C-7 epimerization.

The method involves conversion of the imidoyl chloride 2 into an imine 3 followed by mild hydrolysis to the aminomethoxy compound 4. The key step, the conversion of an imidoyl chloride into a ketimine with a methyl cuprate reagent was reported in the preceeding paper in this Journal Side chain cleavage and transacylation was accomplished according to the outlined scheme.

The imidoyl chloride 2 was conveniently prepared by the reaction of 1 with an excess of phosgene and three molar equivalents of pyridine in CH_2Cl_2 at room temperature for 3 hrs. Filtration, evaporation of the excess phosgene and extraction of the solution with cold aqueous $NaHCO_3$ afforded a solution of the Δ-3 imidoyl chloride 2. The effect of the chlorine was evident when the chemical shifts of the corresponding nuclei were compared in the nmr spectra of 2 and 1. ^1H nmr ($CDCl_3$) $\underline{CH_2}$-C=N, 2.5δ (2.3δ in 1). ^{13}C nmr (CH_2Cl_2 at 0°): $\underline{CH_2}$-C=N- 43.1δ (34.8δ in 1); Cl-C=N- 153.4δ (174.1 in 1).

Reaction of 2 in THF (-15°, 1 hr) with [tBuOCuMe]Li[6] followed by quench with aqueous NH_4Cl-$NaHCO_3$ pH 8 buffer, extraction with CH_2Cl_2 and chromatography[5] afforded aminomethoxy compound 4 in about 50% yield, nmr: ($CDCl_3$) δ 1.9 (s, C_3-$\underline{CH_3}$), 3.5 (s, OCH_3), 3.8 (s, $COO\underline{CH_3}$),



Phth = Phthaloyl

4.8 (br.s. C_4-H), 5.15 (C_6-H), 5.95 (br.s. C_2-H). The side chain ketone 5 was isolated by chromatography, nmr: ($CDCl_3$) δ 1.3-2.6 (m,-CH_2-CH_2-CH_2-), 2.1 (s, CH_3CO-), 4.85 (t, J=7 Hz H-C-COOMe), 7.8 (m, aromatic protons). Acylation of 4 with phenylacetylchloride and pyridine in CH_2Cl_2 at 0° and purification by preparative tlc gave 6a, nmr: ($CDCl_3$) δ 1.9 (s, CH_3), 3.4 (s, CH_3O), 3.7 (m, $\emptyset CH_2$), 3.75 (s, $COOCH_3$), 4.8 (br.s., C_4-H), 5.4 (s, C_6-H), 5.9 (br.s., C_2-H). This material was indistinguishable in its spectral properties from a sample prepared from 1 by direct transacylation[3] followed by $\Delta^3 \rightarrow \Delta^2$ isomerization. Acylation with thienylacetyl chloride afforded 6b.

Double-bond isomerization $\Delta^2 \rightarrow \Delta^3$ is a well documented procedure[7]; therefore, this method could be useful for the preparation of certain 7-methoxycaphalosporins.

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