Short Communications

A New Rearrangement of Cephalosporins in the Presence of Mercury(II) Trifluoroacetate

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The functionalization of the allylic 3-Me group of deacetoxycephalosporins is of great importance for obtaining pharmacologically significant cephalosporins. A well-known procedure is the allylic bromination of deacetoxycephalosporin sulfoxides with subsequent nucleophilic exchange of the bromine into, e.g., –OAc. Another possibility could be the one-step acyloxylation of the 3-Me group by various Pb, Hg, Ti etc. salts. Recently Massiot et al. have found that mercury(II) trifluoroacetate is an excellent reagent for introducing a hydroxy function into steroids.

We have now found that when 1a or b was allowed to react with two equiv. of mercury(II) trifluoroacetate (dry CH₂Cl₂, room temperature, 12 h, aq. NaHCO₃ work-up) an interesting rearrangement occurred leading to 2a or b (m.p.'s: 170 and 167 – 168 °C, resp.).

A similar compound, but having sulfur in lieu of oxygen (3a), was observed first by Morin et al. when phenoxymethylpenicillin sulfoxide methyl ester was heated in the presence of acetic anhydride. The same rearrangement occurs if phenoxymethylpenicillin sulfoxide 4-nitrobenzyl ester is heated in dioxan in the presence of pyridine picrate, yielding 3b, and also when the same sulfoxide 2,2,2-trichloroethyl ester is heated together with acetic anhydride in a toluene – dimethylacetamide mixture giving 3c as the main product. 6

The IR spectra of 2a and b show the presence of two amide NH groups (3365 and 3215 for 2a; 3375 and 3180 for 2b; 3360 and 3164 for 3c) and three C=O groups (1765, 1695 and 1660 cm⁻¹ for 2a; 1776 (sir!) and 1680 (br) cm⁻¹ for 2b; 1750, 1680 and 1660 cm⁻¹ were reported for 3a, similarly 1756, 1688 and 1651 cm⁻¹ were observed for 3c). The mass spectrum of 2a exhibits M⁺ at 404 (four chlorine atoms according to isotopic clusters).

Both of the ¹H NMR spectra (2a: (60 MHz, DMSO-d₆) δ 1.88 (3 H, s), 4.27 (2 H, s), 5.04 (2 H, s), 5.3 – 5.4 (2 H, m), 8.17 (H, s), 9.35 (H, s) and 9.42 (H, s); 2b: δ 1.89 (3 H, s), 4.68 (2 H, s), 5.05 (2 H, s), 5.35 (2 H, s), 6.7 – 7.5 (5 H, m), 8.14 (H, s), 8.97 (H, s) and 9.45 (H, s)) show the disappearance of the β-lactam methine protons and of the 2-CH₂ group and the presence of two olefinic protons at -5.4 (~5.3 for 3a). In the case of 2a they are weakly coupled to the methyl group. The olefinic proton of the other double bond is strongly shifted downfield to δ 8.1 (cf. 3a δ 8.05).

The same conclusions can be drawn from the ¹³C NMR spectra, where the 2-CH₂ and β-lactam CH signals are absent showing two more sp² carbons instead.

* Note added in proof. Wolfe et al. [Can. J. Chem. 53 (1975) 497] reported a compound having the same ring system as in 2 obtained by exposing methyl 2-(2'R-phenylacetox)-3-S-amino-4'-oxoaza tetanyl-3-bromo-methyl-2-butenoate to NET₃. In this case 4b-like intermediary was assumed to form via an O→N acyl transfer.

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Under the same reaction conditions no similar reaction was observed in case of the sulfoxide 1c.

The formation of 2a and b may be understood by assuming that an initial Hg→S attack, assisted by the attack of base at 6-C, opens the dihydrothiazine ring, resulting in an intramolecular β-elimination leading to 4a. This, in turn, is hydrolyzed directly or via 4c followed by a Michael-type addition to the acyl-imine system.

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