

Conversion of 6 α -Alkoxyformamidopenicillanates into 6 α -Aminopenicillanates, and the Formation of 6-Spiropenicillanates

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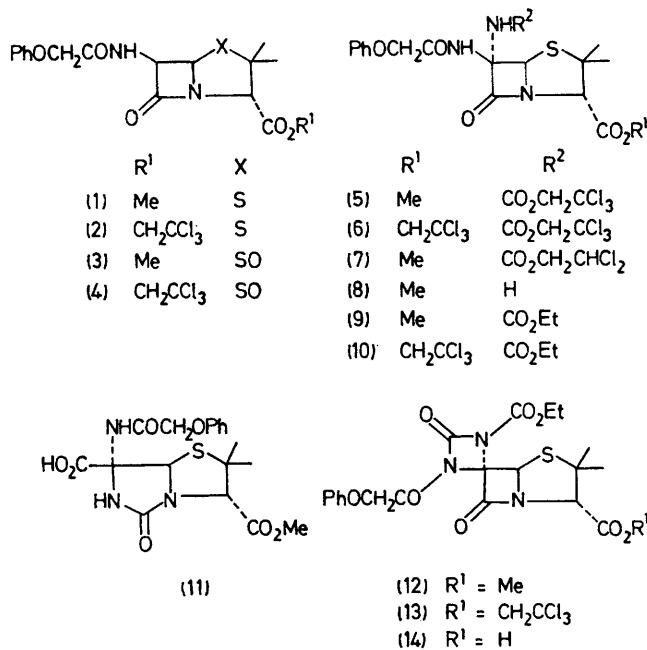
Summary Methyl 6 β -phenoxyacetamido-6 α -trichloroethoxyformamidopenicillanate has been converted into a 6 α -aminopenicillanate; 6 α -ethoxyformamido-6 β -phenoxyacetamidopenicillanates reacted with phosgene and base to afford unique (1-ethoxycarbonyl-3-phenoxyacetyl-2-oxo-1,3-diazetidene)-4-spiro-6'-penicillanates.

(formed by partial reduction of the trichloroethoxy group) and the desired methyl 6 α -amino-6 β -phenoxyacetamidopenicillanate (8),† obtained as an oil (20%), [α]_D²⁰ + 109° (*c* 0.85, CHCl₃). The basic character of (8) was low in that it

IN the search for improved β -lactam antibiotics the introduction of 6 α -substituents into the penam nucleus has been of great importance, as shown by a rapidly increasing number of patents and publications.¹ We have recently described² a method for the introduction of 6 α -alkoxyformamido-groups, and now report developments of this procedure leading to 6 α -aminopenicillanates and novel spiroenicillanates.

It was not feasible to hydrolyse 6 α -ethoxyformamidopenicillanates² to the corresponding 6 α -amino-compounds because of the lability of the β -lactam ring. The reaction of sodium *N*-chloro-2,2,2-trichloroethoxyformamidate³ with the penicillanates (1) and (2) in HCONMe₂ was therefore investigated, and the 6 α -trichloroethoxyformamidopenicillanates (5)† and (6)† were isolated in good yield. [Unchanged starting material which had identical chromatographic retention characteristics to the products was in each case removed, after preferential *m*-chloroperbenzoic acid oxidation, as the sulphoxides (3) and (4).]

Reaction of the trichloroethoxyformamido-group of (5) in Zn-HCONMe₂-AcOH⁴ or in Zn-EtOH-AcOH gave a low yield of non-acidic products containing the 6 α -dichloroethoxyformamido-6 β -phenoxyacetamidopenicillanate (7)†



† Satisfactory elemental analyses and/or molecular ion high-resolution mass measurements were obtained.

was not readily extracted into aqueous acetic acid from ethyl acetate.

The acidic products from the reaction contained as the major product (38%) the thiadiazabicyclo[3.3.0]octane (**11**),[†] m.p. 186—187°, $[\alpha]_D^{20} + 207^\circ$ (*c* 0.54, acetone), which is structurally related to penillic acid,⁵ and is probably formed from a 6 α -carbamic acid intermediate *via* two intramolecular cyclization steps. The 6 α -aminopenicillanate (**8**) did not react with CO₂ to form (**11**), unlike 6 β -aminopenicillanic acid which gives penillic acid with CO₂.⁵ Satisfactory conditions have yet to be developed for the de-esterification and deformylation of (**6**) in order to obtain the amino-acid.

The 6,6-disubstituted penams (**9**) and (**10**) were investigated as potential precursors of spiro- β -lactams.⁶ Thus, (**9**) and (**10**) when treated at -78° in dry tetrahydrofuran

with PhLi (2 equiv.) and excess of phosgene gave in low yield crystalline products tentatively assigned the spiro-1,3-azetidin-2-one structures (**12**)[†] and (**13**).[†] A striking spectroscopic characteristic in each was the intense peak in the i.r. spectrum at 1860 cm⁻¹, together with the less intense β -lactam (1800 cm⁻¹) and ester and amide absorptions. No OH or NH protons were observed in the i.r. or n.m.r. spectra. The n.m.r. spectra were otherwise closely similar to those of (**9**) and (**10**). De-esterification of (**13**)⁴ gave the carboxylic acid (**14**)[†] which was not significantly active as an antibiotic.

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