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

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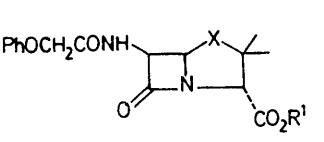
Summary Methyl 6β-phenoxyacetamido-6α-trichloroethoxyformamidopenicillanate has been converted into a 6α-aminopenicillanate; 6α-ethoxyformamido-6β-phenoxyacetamidopenicillanates reacted with phosgene and base to afford unique (1-ethoxycarbonyl-3-phenoxyacetyl-2-oxo-1,3-diazetidine)-4-spiro-6′-penicillanates.

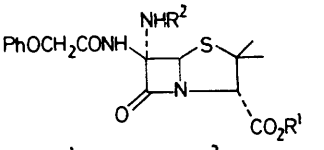
IN the search for improved β-lactam antibiotics the introduction of 6α-substituents into the penam nucleus has been of great importance, as shown by a rapidly increasing number of patents and publications.[1] We have recently described[2] a method for the introduction of 6α-alkoxyformamido-groups, and now report developments of this procedure leading to 6α-aminopenicillanates and novel spiropenicillanates.

It was not feasible to hydrolyse 6α-ethoxyformamidopenicillanates[2] to the corresponding 6α-amino-compounds because of the lability of the β-lactam ring. The reaction of sodium *N*-chloro-2,2,2-trichloroethoxyformamidate[3] with the penicillanates (**1**) and (**2**) in $HCONMe_2$ was therefore investigated, and the 6α-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**).]

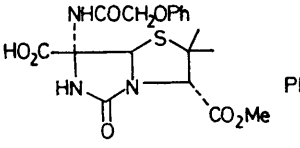
Reaction of the trichloroethoxyformamido-group of (**5**) in Zn–$HCONMe_2$–AcOH[4] or in Zn–EtOH–AcOH gave a low yield of non-acidic products containing the 6α-dichloroethoxyformamido-6β-phenoxyacetamidopenicillanate (**7**)† (formed by partial reduction of the trichloroethoxy group) and the desired methyl 6α-amino-6β-phenoxyacetamidopenicillanate (**8**),† obtained as an oil (20%), $[\alpha]_D^{20}$ + 109° (*c* 0·85, $CHCl_3$). The basic character of (**8**) was low in that it



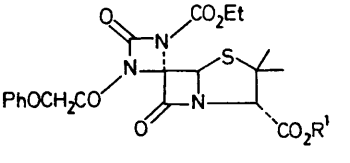
	R^1	X
(1)	Me	S
(2)	CH_2CCl_3	S
(3)	Me	SO
(4)	CH_2CCl_3	SO



	R^1	R^2
(5)	Me	$CO_2CH_2CCl_3$
(6)	CH_2CCl_3	$CO_2CH_2CCl_3$
(7)	Me	$CO_2CH_2CHCl_2$
(8)	Me	H
(9)	Me	CO_2Et
(10)	CH_2CCl_3	CO_2Et



(11)



(12) R^1 = Me
(13) R^1 = CH_2CCl_3
(14) R^1 = H

† 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° (*c* 0·54, acetone), which is structurally related to penillic acid,[5] and is probably formed from a 6α-carbamic acid intermediate *via* two intramolecular cyclization steps. The 6α-aminopenicillanate (**8**) did not react with CO_2 to form (**11**), unlike 6β-aminopenicillanic acid which gives penillic acid with CO_2.[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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