A New Route to 6,6-Disubstituted Penams and 7,7-Disubstituted Cephems

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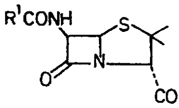
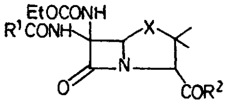
Summary The reaction of penicillanate esters with *N*-chloro-*N*-sodiourethane gave 6,6-diacylaminopenicillanates from which the corresponding 7,7-diacylaminodeacetoxycephalosporanates were prepared *via* the sulphoxides.

RECENT studies of the reactions of penicillanates[1] and secopenicillanates[2] with *N*-chloro-*N*-sodio-toluene-*p*-sulphonamide (chloroamine T) have given reactions which have led to a series of new β-lactams. Mechanisms involving *S*-chlorosulphonium intermediates which underwent subsequent attack by the toluene-*p*-sulphonamidate anion have been described. We have extended these investigations to evaluate the scope and limitations of *N*-chloro-*N*-sodio reagents in the structural modification of penicillanates, and now report that *N*-chloro-*N*-sodio-urethane (**1**)[3] affords totally different products in its reactions.

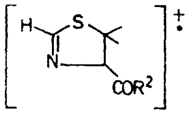
The penicillanates [(**2**)—(**4**)] reacted readily in acetonitrile at room temperature with excess (**1**) to give, in each case, one major reaction product, (**5**)—(**7**), (80—90% yield). For example, methyl 6β-phenoxyacetamidopenicillanate (**2**) gave a crystalline solid, m.p. 142—5°, $[\alpha]_D^{20} = +56°$ (c 1·00, $CHCl_3$), shown by elemental analysis and molecular ion mass measurement to have the formula $C_{20}H_{25}N_3SO_7$, indicating incorporation of the urethane group into the penam. Structure (**5**)† was strongly suggested from the spectroscopic data, [i.r. (KBr) 1780, 1740, 1725 and 1680 cm^{-1}, n.m.r. (CDCl$_3$) τ 2·0 and 3·75 (2× br s, solvent and concentration dependent, not exchanged in D$_2$O but slowly removed in D$_2$O–D$_2$SO$_4$, two amide protons), 4·32 (sharp s, single β-lactam H), 5·53 (H-3), 8·55 and 8·62 (*gem*-dimethyl)] and phenoxyacetamido, ethoxyformamido and carbomethoxy groups; the mass spectra of [(**5**)—(**7**)] exhibited an intense ion of structure (**15**). The trichloroethyl ester (**7**) was converted in high yield into the 6,6-disubstituted penicillanic acid (**8**) in dimethylformamide (DMF)–acetic acid–Zn[4] at 0°.



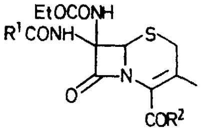
(2); R^1 = PhOCH$_2$, R^2 = OMe
(3); R^1 = PhCH$_2$, R^2 = NHBu^t
(4); R^1 = PhOCH, R^2 = OCH$_2$CCl$_3$



(5); R^1 = PhOCH$_2$, R^2 = OMe, X = S
(6); R^1 = PhCH$_2$, R^2 = NHBu^t, X = S
(7); R^1 = PhOCH$_2$, R^2 = OCH$_2$CCl$_3$, X = S
(8); R^1 = PhOCH$_2$, R^2 = OH, X = S
(9); R^1 = PhOCH$_2$, R^2 = OMe, X = SO
(10); R^1 = PhCH$_2$, R^2 = NHBu^t, X = SO
(11); R^1 = PhOCH$_2$, R^2 = OCH$_2$CCl$_3$, X = SO
(12); R^1 = PhOCH$_2$, R^2 = OCH$_2$CCl$_3$, X = SO$_2$



(15)



(13); R^1 = PhOCH$_2$, R^2 = OCH$_2$CCl$_3$
(14); R^1 = PhOCH$_2$, R^2 = OH

The sulphoxides [(**9**)—(**11**)] were prepared by *m*-chloroperbenzoic acid oxidation, (**9**) and (**10**) being obtained as a mixture of *R*- and *S*- sulphoxides, possibly indicating that the incoming oxidant was being directed by either the 6α- or 6β-amido group (6β-acylaminopenicillanates give principally the β-sulphoxide[5]). Excess oxidant led rapidly to the sulphone (**12**). Treatment of (**11**) in DMF–acetic anhydride at 130°[4] gave the 7,7-disubstituted deacetoxycephalosporanate (**13**) (50%), $[\alpha]_D^{20}$ + 23° (*c* 1·00, CHCl$_3$); ν_{max}(KBr) 1790 and 1730—1670 cm^{-1}; λ_{max} 265 nm (ϵ 6800); τ(CDCl$_3$) 2·00 and 3·20 (each 1H, br, s, slowly exchanged by D$_2$O–D$_2$SO$_4$, two amide protons), 4·83 (1H, s, H-6), 7·10 (2H, dd, *J* 15 Hz, –S–C*H*$_2$–); in the mass spectrum of (**13**) an intense peak corresponding to a thiazine cation was observed, further supporting the proposed structure. Ester (**13**) was converted into the novel 7,7-disubstituted deacetoxycephalosporanic acid (**14**) (77%) in DMF–acetic acid–Zn.[4]

This method gives a simple preparation of 6,6-disubstituted penams and 7,7-disubstituted cephems which are of current interest.[6] The detailed stereochemistry of these compounds will be reported following completion of an *X*-ray crystallographic investigation of (**5**).

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† All new compounds gave correct elemental analyses and/or molecular ion high resolution mass measurements.

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