# Formation of Enantiomeric 4-Oxa-2,6-diazabicyclo[3.2.0]hept-2-en-7-ones† from Methyl 6α- and 6β-Phenoxyacetamidopenicillanates

By **Malcolm M. Campbell** * and **Graham Johnson**, Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Midlothian

Methyl 6α-phenoxyacetamidopenicillanate was transformed by reaction with chloramine T or (dichloroiodo)-benzene into methyl 3-methyl-2-[(1*R*,5*S*)-3-phenoxymethyl-7-oxo-4-oxa-2,6-diazabicyclo[3.2.0]hept-2-en-6-yl]but-2-enoate. The (1*S*,5*R*)-isomer was prepared by the reaction of (dichloroiodo)benzene with methyl 6β-phenoxyacetamidopenicillanate. Differences in the reactivities of the 6α- and 6β-acylaminopenicillanates towards chloramine T and (dichloroiodo)benzene are noted.

PREVIOUSLY [1,2] we have described reactions of chloramine T (sodium *N*-chlorotoluene-*p*-sulphonamidate trihydrate) with 6β-amidopenicillanates [*e.g.* (1)] to give β-lactam-fused thiadiazine *S*-imides (2). Participation of the 6β-acylamino-group in a mechanism involving formation of an intermediate *S*-chlorosulphonium adduct was presumed. We have now examined the corresponding reactions of chloramine T with the 6α-amidopenicillanate (3), in order to ascertain the mode of reaction in systems in which the acylamino-unit is *trans* to the sulphur group.

Accordingly the 6α-amidopenicillanate (3), prepared by the method of Vlietinck,[3] was treated at room temperature in methanol with chloramine T (2.5 mol. equiv.). T.l.c. indicated rapid build-up of a polar product which was gradually transformed into one of lesser polarity. Chromatography afforded the less polar product ‡ in low yield as an oil, $[\alpha]_D^{20}$ −20° (*c* 1.00 in $CHCl_3$), which was shown to be the oxazoline-fused azetidinone (4) by spectroscopic analysis. A higher yield of compound (4) with $[\alpha]_D^{20}$ −19° was obtained by the reaction of an excess of (dichloroiodo)benzene–aqueous pyridine [4] with the 6α-amidopenicillanate (3). [(*R*)- and (*S*)-*S*-oxides were also obtained.] The product (4) appeared to be of opposite chirality to previously reported (1*S*,5*R*)-oxadiazabicycloheptenones.[4,5]

To establish the absolute stereochemistry of (4) we therefore prepared the (1*S*,5*R*)-compound (5) by the Barton route,[4] from methyl 6β-phenoxyacetamidopenicillanate and an excess of (dichloroiodo)benzene in aqueous pyridine. The product showed $[\alpha]_D^{20}$ +18° (*c* 1.00 in $CHCl_3$) and the n.m.r. and i.r. spectra of compounds (4) and (5) were identical.

The formation of (4) in the reaction of chloramine T with the 6α-amidopenicillanate (3) can therefore be explained (Scheme 1) in terms of a stereochemically favoured intramolecular *trans* displacement from a chlorosulphonium intermediate (6) yielding a sulphenyl halide (7). Alternatively, the intermediate (6) may be transformed into an aminosulphonium or sulphimide system which undergoes a similar elimination process. In the reaction of (dichloroiodo)benzene with the penicillanate (3), a *trans* displacement process possibly also occurs as in Scheme 1, whereas in the corresponding reaction of (dichloroiodo)benzene with the enantiomer (1) the intermediates (8) and (9) may be involved (Scheme 2). It is probable that in the enantiomers (4) and (5) the butenoate group adopts a *trans*-configuration relative to the oxazo-

† The Editor regrets that in some previous papers in *J.C.S.* this system was incorrectly referred to as 2-oxa-4,7-diazabicyclo-[3.2.0]hept-3-en-6-one.

‡ The more polar product was eluted as an inseparable mixture of unstable β-lactams formed by on-column reactions. N.m.r. analysis indicated the possible presence of an oxazoline sulphenamide which could be derived by displacement of chloride from (7) by toluene-*p*-sulphonamidate ion.

[1] M. M. Campbell, G. Johnson, A. F. Cameron, and I. R. Cameron, *J.C.S. Chem. Comm.*, 1974, **868**; M. M. Campbell and G. Johnson, *ibid.*, p. 974.

[2] M. M. Campbell and G. Johnson, *J.C.S. Perkin I*, 1975, 1208.

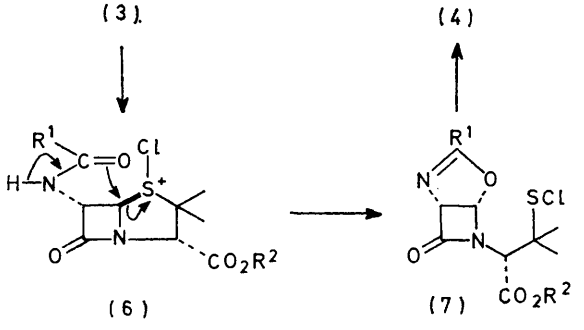
[3] A. J. Vlietinck, E. Roets, H. Vanderhaeghe, and S. Toppet, *J. Org. Chem.*, 1974, **39**, 441.

[4] D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

[5] (*a*) J. C. Sheehan in 'Molecular Modifications of Drug Design,' A.C.S. Advances in Chemistry Series, No. 45, Washington, D.C., 1964, p. 15; (*b*) E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1972, 229; (*c*) R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181; (*d*) D. F. Corbett and R. J. Stoodley, *ibid.*, p. 185.

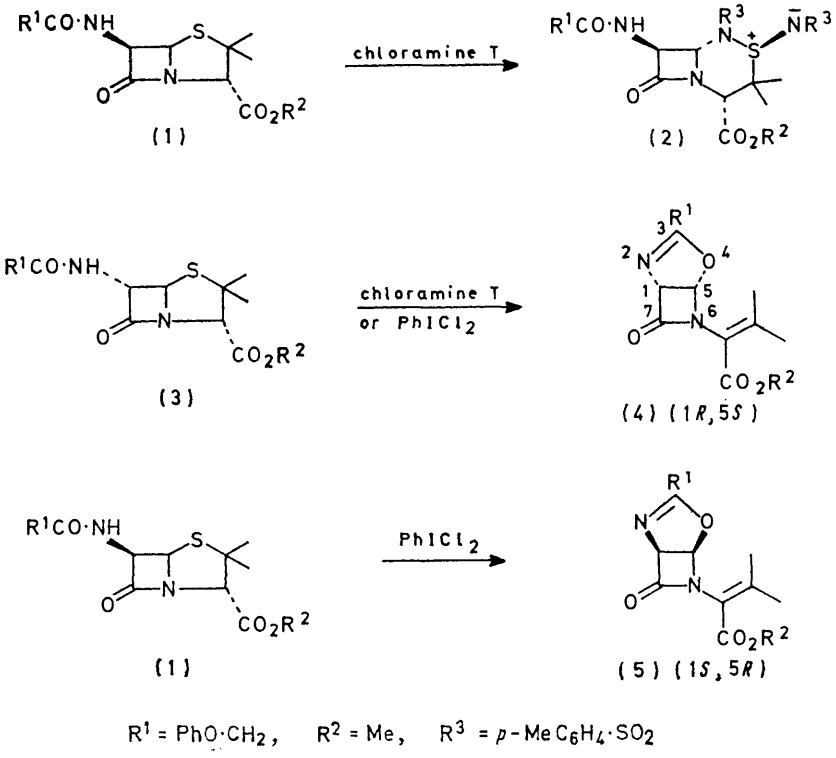
line ring, implying that in the pathway to (5) (Scheme 2) inversion at the β-lactam nitrogen atom * occurs readily following formation of (9). Another reaction pathway from (6) or (8) would involve initial cleavage of S–C(2) bond with concomitant elimination of H-3, affording a 4-chlorosulphenylazetidinone which could lead to (4) or (5).

An earlier publication [2] indicated that in the reactions of certain † 6β-acylaminopenicillanates with chloramine T the acylamino-group was involved in the formation of chlorosulphonium species which were then transformed into *S*-imides (2), possibly by the reaction of an intermediate such as (9) with toluene-*p*-sulphonamidate anion.



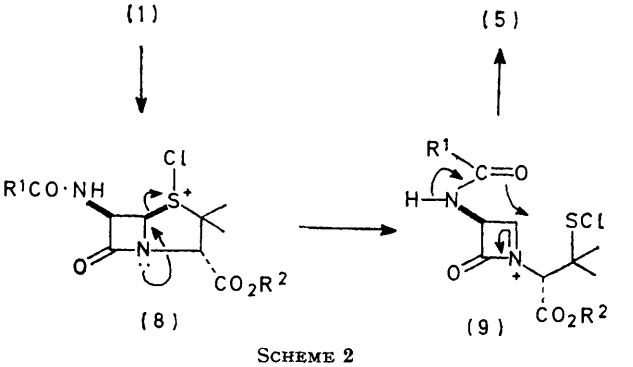

SCHEME 1

The present study shows that chloramine T and a 6α-acylaminopenicillanate participate in a more complex reaction from which a (1*R*,5*S*)-oxadiazabicycloheptenone can be isolated, a chlorosulphonium intermediate again being involved. Different modes of involvement of the acylamino-group in 6β- and 6α-amidopenicillanates have thus been demonstrated for the chloramine T reactions.




$R^1$ = PhO·$CH_2$, $R^2$ = Me, $R^3$ = *p*-Me$C_6H_4$·$SO_2$

(Dichloroiodo)benzene, however, affords enantiomeric oxazolines in its reactions with a 6α- and a 6β-amidopenicillanate.




SCHEME 2

## EXPERIMENTAL

General details are as described in ref. 2. *Reaction of Methyl-6α-Phenoxyacetamidopenicillanate* (3) *with Chloramine* T.—To a solution of compound (3) (1.17 g, 0.03 mol) in methanol (25 ml) at room temperature was added chloramine T (1.83 g, 0.07 mol) in methanol (25 ml). The solution was stirred for 45 min. T.l.c. indicated rapid build-up of a polar product which was gradually transformed into a less polar product. After partitioning between ethyl acetate

* A variable-temperature n.m.r. study of compound (4) between −60 and 100 °C of inversion about nitrogen later showed no significant changes.

† 6β-Phthalimido, 6β-triphenylmethylamino, and 6,6-dibromopenicillanates did not react, showing the necessity of the 6β-(secondary amido)-group.

and dilute aqueous sodium hydroxide, the ethyl acetate layer was dried ($MgSO_4$) and evaporated *in vacuo* to yield an oil (1.19 g). Chromatography afforded, as an oil, *methyl* 3-*methyl*-2-{(1R,5S)-3-*phenoxymethyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*}*but*-2-*enoate* (4) (0.20 g, 24%), $[\alpha]_D^{20}$ −20° (*c* 1.00 in $CHCl_3$), $\lambda_{max.}$ (film) 1 785 (β-lactam C=O), 1 730 (ester C–O), and 1 660 $cm^{-1}$ (oxazoline C=N), τ ($CDCl_3$) 8.14 (3 H, s) and 7.80 (3 H, s) (2 × Me), 6.17 (3 H, s, MeO), 5.17 (2 H, s, PhO·$CH_2$), 4.75 (1 H, d, *J* 4 Hz, 1-N), 3.85 (1 H, d, *J* 4 Hz, 5-H), and 3.20—2.60 (5 H, m, PhO) (Found: $M^+$, 330.1213. $C_{17}H_{18}N_2O_5$ requires *M*, 330.1216). Despite repeated attempts, the polar β-lactam constituents of the reaction mixture could not be isolated pure because of on-column reactions. Different ratios of reagents were investigated, the conditions described above affording the best yield of (4). Similar products were obtained in acetonitrile as solvent.

*Reaction of Methyl*-6β-*Phenoxyacetamidopenicillanate* (1) *with* (*Dichloroiodo*)*benzene*.—To a solution of compound (1) (0.68 g, 0.02 mol) in pyridine (16 ml) was added water (2 ml), and the solution was cooled to −14°. A solution of (dichloroiodo)benzene (1.6 g, 0.06 mol) in pyridine (16 ml) was added dropwise over 10 min. After stirring for 1.5 h at −14 °C the solution was diluted with ethyl acetate (100 ml), washed with M-sulphuric acid and water, dried ($MgSO_4$), and evaporated *in vacuo* to yield an oil. Chromatography afforded, as an oil, *methyl* 3-*methyl*-2-[(1S,5R)-3-*phenoxymethyl*-7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3.2.0]*hept*-2-*en*-6-*yl*]*but*-2-*enoate* (5) (0.10 g, 16%), $[\alpha]_D^{20}$ +18° (*c* 1.00 in $CHCl_3$), n.m.r. and i.r. spectra identical with those of (4) apart from the presence of a trace impurity of identical $R_F$ in (4) (Found: $M^+$ 330.1216). Further elution afforded the (*R*)- and (*S*)-*S*-oxides as the major products.

*Reaction of Methyl* 6-α-*Phenoxyacetamidopenicillanate* (3) *with* (*Dichloroiodo*)*benzene*.—A solution of compound (3) (0.82 g, 0.02 mol) was treated with (dichloroiodo)benzene (1.93 g, 0.07 mol) as described above. Chromatography afforded the oxazoline (4) as an oil (0.24 g, 32%), $[\alpha]_D$ −19° (*c* 1.00 in $CHCl_3$), n.m.r. and i.r. spectra identical with those of (4). Further elution of the column afforded an inseparable mixture of the (*R*)- and (*S*)-*S*-oxides as an amorphous solid (0.25 g, 29%) (ratio of isomers, by n.m.r., 5 : 1) [Found: $M^+$ (mixture), 380.1033. Calc. for $C_{17}H_{20}N_2O_6$: *M* 380.1042].

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