On the Trapping of Sulphenic Acids from Penicillin Sulphoxides

By D. H. R. BARTON,* D. G. T. GREIG, G. LUCENTE, P. G. SAMMES, and M. V. TAYLOR
(*Chemistry Department, Imperial College, London, S.W.7*)
and (MRS.) C. M. COOPER, G. HEWITT, and W. G. E. UNDERWOOD
(*Glaxo Research Limited, Greenford, Middlesex*)

Summary The intermediate sulphenic acids produced thermally from penicillin sulphoxides can be trapped either intramolecularly, as in the rearrangement of the 2β-acetoxymethyl derivatives into the 2α-acetoxymethyl isomers, or intermolecularly with norbornadiene or dihydropyran.

THE suggested existence of sulphenic acid intermediates on heating penicillin sulphoxides[1] has recently been confirmed both by deuterium trapping[2] and reductive methods.[3] In particular, it was noted that the (*R*)-sulphoxide (**1**) rearranged into the (*S*)-sulphoxide (**2**) on warming.[4] Since opening of the thiazolidine ring occurs stereospecifically by a *cis*-type sigmatropic reaction and recyclisation occurs towards the β-face of the molecule (*e.g.* **3**) rotation about the C-2–C-3 bond must occur during isomerisation. This was demonstrated in the acetoxy-substituted series. Oxidation of the 2β-acetoxymethylpenam (**4**), m.p. 118—119°, $[\alpha]_D^{25}$ + 151° (*c* 1, $CHCl_3$), with iodobenzene dichloride in aqueous pyridine[5] gave both the (*R*)-sulphoxide (**5a**), $[\alpha]_D^{20}$ + 137 (*c* 1, $CHCl_3$) and its (*S*)-isomer (**6**),† $[\alpha]_D^{20}$ + 184° (*c* 1, $CHCl_3$) as shown by ^1H n.m.r. spectroscopy (see Table).[6] Heating the (*R*)-sulphoxide (**5a**) in toluene rapidly gave an isomeric sulphoxide different from the (*S*)-sulphoxide (**6**). This was shown by its ^1H n.m.r. properties (see Table) to be the new (*S*)-sulphoxide (**7a**), $[\alpha]_D^{20}$ + 181° (*c* 1, $CHCl_3$). These reactions could also be repeated in the *p*-nitrobenzyl ester series, the sulphoxide (**5b**), $[\alpha]_D^{20}$ + 95° (*c* 1, tetrahydrofuran) giving the (*S*)-sulphoxide (**7b**), $[\alpha]_D^{25}$ + 118° (*c* 1, tetrahydrofuran).

^1H *N.m.r. values*

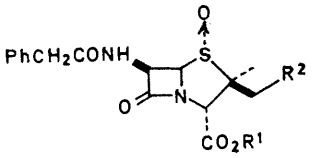
Group	(4)	(5a)	(6)	(7a)	(8)[b]
Me	8·48	8·62	8·73	8·30	8·51
$AcOCH_2$[c]	5·67,6·32(12)	5·40	5·26,5·52(12)	5·43,6·02(12·5)	5·88,5·94(13)
3-H	5·25	5·25	5·18	5·20	5·52
5-H	4·41(4)	5·21(4)	5·05(4)	4·98(4)	4(52(4·5)
6-H	4·32(4, 11)	4·82(4, 11)	3·99(4,9)	3·94(4,9)	4·37(4·5,10)

[a] Recorded as τ values on a Varian A60 instrument in $CDCl_3$ with Me_4Si as internal reference.
[b] A *p*-nitrobenzyl ester; all others as trichloroethyl esters.
[c] AB quartets: where split, midpoints of signals taken without correction.

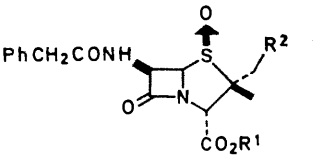
Reduction of the latter sulphoxide with phosphorus tribromide in *NN*-dimethylformamide at 0° for 10 min[7] gave the 2α-acetoxymethylpenam (**8**) as a foam. Direct hydrogenolysis[8] of this product gave the corresponding acid, isolated as its sodium salt trihydrate, $[\alpha]_D^{23}$ + 218° (*c* 1, H_2O) ν_{max} (Nujol) 1770 (β-lactam), 1735 (acetate), 1655, 1535

† All new compounds gave satisfactory microanalyses.

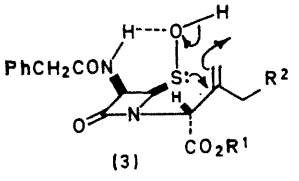
(amide), 1615 (CO_2^-) cm^{-1}, a member of a new family of substituted penicillins.‡



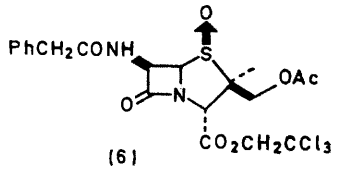
(1) R^1 = Me, R^2 = H
(5a) R^1 = CH_2CCl_3, R^2 = OAc
(5b) R^1 = p-$NO_2C_6H_4CH_2$-, R^2 = OAc



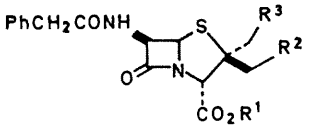
(2) R^1 = Me, R^2 = H
(7a) R^1 = CH_2CCl_3, R^2 = OAc
(7b) R^1 = p-$NO_2C_6H_4CH_2$, R^2 = OAc



(3)

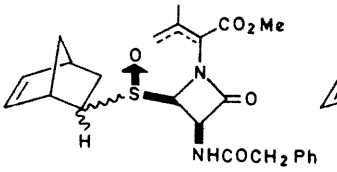


(6)

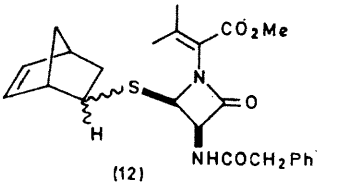


(4) R^1 = CH_2CCl_3, R^2 = OAc, R^3 = H
(8) R^1 = p-$NO_2C_6H_4CH_2$, R^2 = H, R^3 = OAc
(9) R^1 = R^2 = H, R^3 = OAc

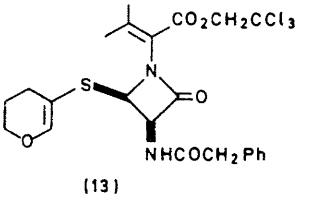
Because the observed rotation about the C-2–C-3 bond during the above isomerisation requires a relatively long-lived sulphenic acid intermediate, more standard trapping experiments were attempted.[9] Heating the penicillin (*S*)-sulphoxide (2) in benzene containing norbornadiene gave one major, non-crystalline, unstable adduct, isomerised by triethylamine into a crystalline $\alpha\beta$-unsaturated ester, m.p.



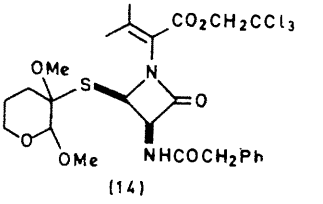
(10) $\beta\gamma$-isomer
(11) $\alpha\beta$-isomer



(12)



(13)



(14)

147—151°, $[\alpha]_D^{20}$ + 89·5° (*c* 1, $CHCl_3$). The presence of the β-lactam moiety was inferred from its i.r. absorption, ν_{max} 1780 (lactam) cm^{-1} and characteristic ^1H n.m.r. pattern with substituent protons at τ 4·85 (d, 1H, *J* 4 Hz) and 4·18 (dd, 1H, *J* 4 Hz).[10] The crystalline adduct was therefore assigned structure (**11**) and its unstable precursor as the $\beta\gamma$-isomer (**10**). Reduction of (**11**) with phosphorus tribromide in dimethylformamide gave the corresponding sulphide (**12**), m.p. 135°, $[\alpha]_D^{24}$ — 10·9° (*c* 1, $CHCl_3$).

An alternative trapping experiment on the trichloroethyl ester (**2**); $R^1 = CH_2CCl_3$, $R^2 = H$) using dihydropyran (preferably with aluminium tribromide as catalyst), followed by treatment with triethylamine, afforded one crystalline product, m.p. 116—117°, $[\alpha]_D^{25}$ + 59° (*c* 1, $CHCl_3$), analysed as a 1 : 1 adduct with loss of the elements of water. The product readily afforded two sulphoxides by oxidation with sodium periodate ($[\alpha]_D^{20}$ + 161° and $[\alpha]_D^{20}$ + 8° both at *c* 1, tetrahydrofuran), and its ^1H n.m.r. spectrum was consistent with the vinyl sulphide (**13**). This sulphide must be formed by electrophilic attack by the sulphenic acid intermediate on to the double bond of dihydropyran. The product was unaffected by treatment with methanolic hydrochloric acid or by mercuric chloride.[11] Oxidation with bromine in methanol gave the expected dimethoxy-derivative (**14**).

(*Received, October 27th*, 1970; *Com.* 1869.)

‡ The sodium salt of the acid (**9**) had a minimum inhibitory concentration against *Staphylococcus aureus* 663 of 0·16 mcg/ml.

[1] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1963, **85**, 1896; *ibid.*, 1969, **91**, 1401.
[2] D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059; R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.
[3] R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[4] D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1969, **91**, 1529.
[5] G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.* (*C*), 1968, 659.
[6] *Cf.* R. D. G. Cooper, P. V. De Marco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408; R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and C. L. Spangle, *J. Chem. Soc.* (*C*), 1970, 340.
[7] *Cf.* G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.
[8] F. H. Carpenter and D. T. Gish, *J. Amer. Chem. Soc.*, 1952, **74**, 3818.
[9] *Cf.* J. A. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 218.
[10] G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1965, 1595; K. D. Barrow and T. M. Spotswood, *Tetrahedron Letters*, 1965, 3325.
[11] D. I. MacDonald and H. G. Fletcher, *J. Amer. Chem. Soc.*, 1959, **81**, 3719.