

## Rearrangements of Penicillin Sulphoxides

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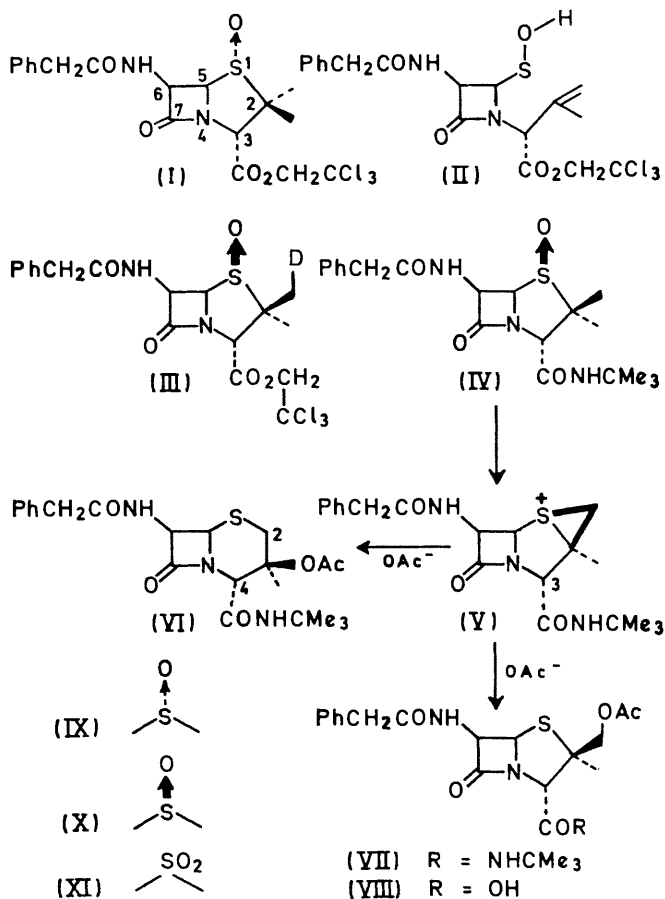
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**Summary** Isomerisation of a penicillin G (*R*)-sulphoxide into the corresponding (*S*)-isomer proceeds by a sulphenic acid intermediate which has been trapped by deuterium incorporation; in the rearrangement of the *t*-butylamides of the (*S*)-sulphoxide of penicillin G only cepham and penam derivatives are isolated and no cephem products are formed.

WE recently reported on the thermal isomerisation of the penicillin (*R*)-sulphoxide (I) to give the corresponding (*S*)-sulphoxide.<sup>1</sup> This isomerisation has now been shown to proceed *via* the sulphenic acid intermediate (II). Heating the (*R*)-sulphoxide in Bu<sup>4</sup>OD<sup>2</sup> at 80° for 3 h gave, principally, the (*S*)-sulphoxide. After renormalisation of the side-chain amide proton with methanol, mass spectroscopy indicated the incorporation of one deuterium atom (60%). <sup>1</sup>H n.m.r. spectroscopy showed that this was specifically sited in the lower-field, 2β-methyl group (III).<sup>3</sup> A control experiment on the (*S*)-sulphoxide showed no significant deuterium incorporation after 3 h. The specific substitution by only one deuterium atom can only be explained by the intermediate discrete formation of the sulphenic acid (II). That the (*S*)-sulphoxide is preferred in the recyclisation step implies that the sulphenic acid intermediate also prefers to deliver its proton on the β-face of the molecule, as shown by n.m.r. spectroscopy (see above). This is possibly due to hydrogen bonding with the side-chain amide proton. The thermal 6-electron sigmatropic reactions of sulphoxides has precedent.<sup>4</sup>

In the presence of dehydrating agents, such as acetic anhydride, the sulphenic acid can form a mixed anhydride susceptible to intramolecular nucleophilic attack by the double bond to form intermediate sulphonium ions (*e.g.*, V). With esters the 3β-proton can be lost from (V) to give the cephem derivatives. Alternatively, rearrangement before sulphonium ion formation to give the less reactive uncyclised αβ-double-bond isomer<sup>5</sup> is possible. Similarly the free acid corresponding to the sulphonium ion [as (V)] can decarboxylate. However in an amide derivative the enolisability of the 3β-proton would be lowered, thus favouring quenching of the sulphonium intermediate by external nucleophiles such as acetate ions. This was observed in the rearrangement of the *t*-butylamide (IV)<sup>6</sup>, m.p. 171–174°, [α]<sub>D</sub> + 225° (*c* 1.0, THF), which, with acetic anhydride, gave mainly a 3:1 mixture of two products. The major compound was the cepham derivative (VI) isolated by repeated crystallisation, m.p. 243–248° (decomp.), [α]<sub>D</sub> + 42° (*c* 1.0, THF). The minor isomer was the non-crystalline penam acetate (VII), identical to a sample prepared from the acid (VIII). The structure of the cepham derivative was arrived at from its physical properties. Its n.m.r. spectrum (see Table) showed the methylene protons at position 2 as an AB quartet (*J* 14 Hz) with long-range coupling of the higher-field proton to that at position 4, caused by the planar

zig-zag conformation between these protons,<sup>7</sup> whilst its i.r. spectrum showed the β-lactam carbonyl at ν<sub>max</sub> 1760 cm.<sup>-1</sup> In contrast, the penam derivative (VII) showed the acetoxy-methylene protons as an AB quartet τ 5.73, 6.04 (*J* 12.5 Hz) with no long-range coupling and with ν<sub>max</sub> 1792 cm.<sup>-1</sup> for the β-lactam carbonyl. The *cis*-disposition of the acetoxy-group to the 4β-proton in the cepham compound (VI) was



confirmed by the observed small Nuclear Overhauser effect<sup>3</sup> (5% enhancement on irradiating the 3α-methyl group). The stereochemistry of the products (VI and VII) is determined by the opening of the sulphonium-ion intermediate (V) which must also be β-oriented as shown. The structure of the cepham compound (VI) was further supported by oxidation to its two sulphoxides, both of which gave the same sulphone (see Table) on further oxidation. The (*S*)-sulphoxide (X; β-configuration) was the principal product from the perchthalic acid oxidation of the cepham (VI) whilst oxidation with sodium periodate gave, principally, the (*R*)-sulphoxide (IX; α-configuration).

Group	<sup>1</sup> H n.m.r. values <sup>a</sup>			
	(vi)	(ix)	(x)	(xi)
3-CH <sub>3</sub>	8.46	8.35	8.42	8.43
-CH <sub>2</sub> S- <sup>b</sup>	6.25 ABq (14)	6.20 ABq(14)	5.67 ABq(15)	5.93 ABq(14)
	6.80	6.70	6.65	6.10
4-H	5.60	5.10	5.40	5.56
6-H	4.70d(4.5)	5.16d(4.5)	5.03d(4.5)	4.86d(4.6)
7-H <sup>c</sup>	4.42dd(4.5,9)	4.73dd(4.5,8)	4.00dd(4.5,10)	4.01dd(4.5,10)

<sup>a</sup> As  $\tau$  values, in CDCl<sub>3</sub> with Me<sub>4</sub>Si as internal reference; measured on a Varian HA100 instrument; d, doublet, q, quartet.

<sup>b</sup> Observed midpoints quoted, not calculated values.

<sup>c</sup> Comparable downfield shifts are observed for the corresponding proton in the penam series.<sup>1</sup>

The structure of the latter compound was further confirmed by an X-ray crystallographic analysis of the related *p*-bromophenylacetyl derivative (IX; with *p*-Br substitution in the phenyl ring),<sup>8</sup> m.p. 223–225° (decomp.), [ $\alpha$ ]<sub>D</sub> – 45° (c 0.1, CHCl<sub>3</sub>), prepared by standard methods commencing with 6 $\beta$ -(*p*-bromophenyl)acetamidopenicillanic acid.

The incorporation of deuterium into the 2 $\beta$ -methyl group of a penicillin (*S*)-sulphoxide has also been observed by Dr. R. D. G. Cooper, whom we thank for his courtesy in forwarding the relevant manuscript copy.

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<sup>2</sup> M. Morton, J. A. Cala, and J. Dissma, *J. Amer. Chem. Soc.*, 1956, **78**, 5394.

<sup>3</sup> Cf. R. D. G. Cooper, P. V. DeMarco, 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. A. Spangle, *J. Chem. Soc. (C)*, 1970, 340.

<sup>4</sup> J. A. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 218; R. D. G. Cooper and F. L. José, *ibid.*, 1970, **92**, 2575.

<sup>5</sup> R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401.

<sup>6</sup> All new compounds had satisfactory microanalytical and spectral properties.

<sup>7</sup> Cf. L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon, Oxford, 1969, p. 334.

<sup>8</sup> See accompanying communication, by M. L. Smart and D. Rogers.