Transformation of Penicillin Sulphoxides into Cephalosporins by Azo-compounds

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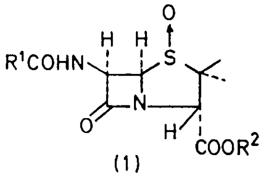
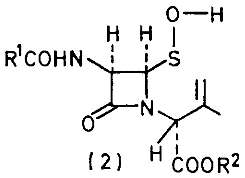
Summary Treatment of penicillin sulphoxides with azo-compounds gave cephems (**3**) in moderate yields together with sulphinyl hydrazodicarboxylates (**4**) and thiol sulphonates (**5**).

PENICILLIN sulphoxides have been previously[1] converted into cephalosporins with acid catalysts. We have effected the same transformation under non-acidic conditions, using azo-compounds.

Treatment of the methyl ester of penicillin V sulphoxide (**1a**) with diethyl azodicarboxylate (1 mol. equiv.) in refluxing dioxan gave products which were separated by silica-gel chromatography and identified† as compound (**3a**) (25·9%), m.p. 141—142°, (**4**) (14·2%), $C_{23}H_{30}N_4O_{10}S$, non-crystalline solid, (**5**) (11·3%), $C_{34}H_{38}N_4O_{12}S_2$, m.p. 58—159°, $[\alpha]_D^{23}$ −61·1° (*c* 1·5 in $CHCl_3$), and diethyl hydrazodicarboxylate. Attempts to transform (**4**) and (**5**) into (**3**) were unsuccessful under various conditions. The reaction of (**5**) with 1,1-dimethylethanethiol gave the mixed disulphide (**6**),‡ $C_{21}H_{28}N_2O_5S_2$, m.p. 114°, $[\alpha]_D^{23}$ −211·5° (*c* 1·25 in $CHCl_3$).


(1)

	R^1	R^2
(a)	CH_2OPh	Me
(b)	CH_2OPh	$C_2H_4SO_2Me$
(c)	CH_2Ph	Me
(d)	CH_2Ph	$C_2H_4SO_2Me$
(e)	CHPh NH $CO_2C_2H_4SO_2Me$	Me
(f)	CHPh NH $CO_2C_2H_4SO_2Me$	$C_2H_4SO_2Me$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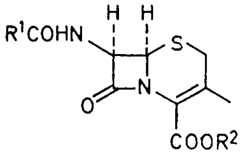
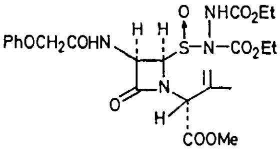
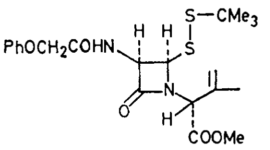
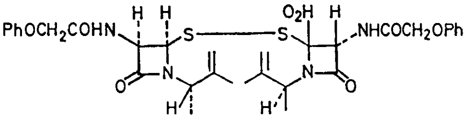

(3)

The yields of the products are greatly affected by the azo-compounds used and reaction conditions such as temperature, solvent, and concentration, but less affected by the species of penicillin sulphoxide.

Azo-compounds[2] which contain one carbonyl group (R–N=N–COR′, R–N=N–COOR′) or two carbonyl groups (R-CO-N=N-CO-R′, ROCO-N=N-COOR′) and/or one phosphono-group [R–N=N–P(:O)(OR′)$_2$] adjacent to the azo-group all effected similar reactions.


(4)


(6)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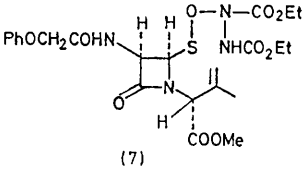
(7)

When α,α′-azobis-(*N*-methylformamide) was used in dimethylacetamide at 100—110°, esters of penicillin sulphoxides (**1a—f**) afforded the corresponding cephems (**3a—f**) in 30—40% yields.

The reaction probably proceeds *via* intermediate (**7**) which would then be rapidly converted into (**3**), (**4**), and (**5**) along three competing reaction routes.

The optimum conditions for the conversion of (**1**) into (**3**) are now being investigated.

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† The composition of all new compounds was confirmed by elemental analysis or by mass spectroscopy. Structural assignments are based on i.r. and n.m.r. spectral evidence.

‡ The disulphide (**6**) was prepared by a new disproportionation reaction of penicillin sulphoxides with disulphides, and will be published elsewhere.

[1] D. H. R. Barton and P. G. Sammes, *Proc. Roy. Soc.*, 1971, **179**, 345; 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; 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.

[2] E. Fahr and H. Lind, *Angew. Chem. Internat. Edn.*, 1966, **5**, 372.