Multiple Rearrangements of Penicillin Sulphoxides

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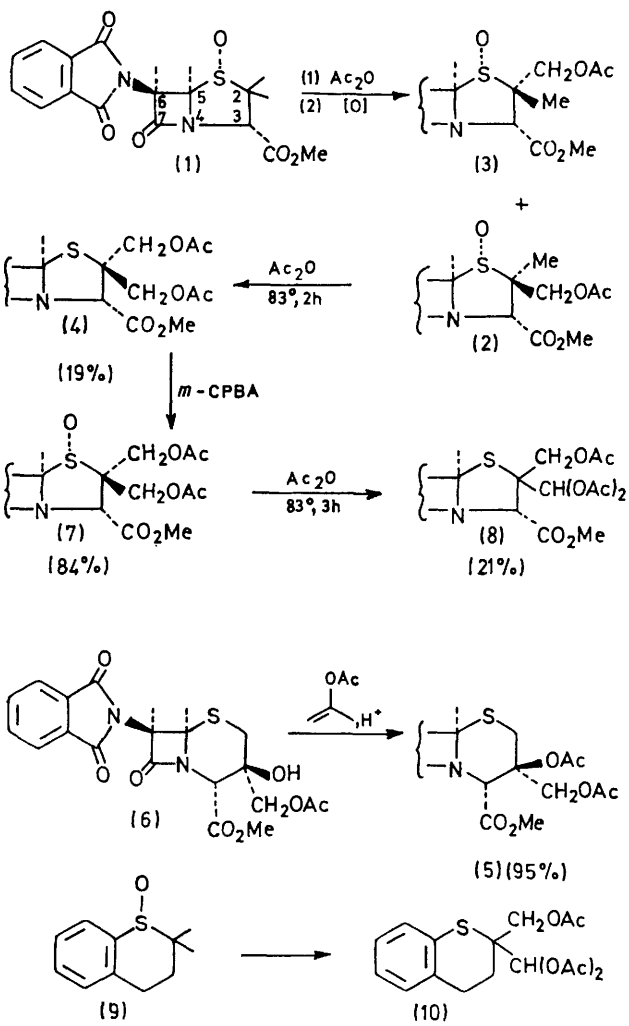
Summary Multiple rearrangements of phthalimidopenicillin 1-oxide with acetic anhydride result in 2-*C*-bisacetoxymethyl- and 2-*C*-triacetoxy-penicillin derivatives.

MORIN *et al.*[1] have reported the reaction of phenoxymethylpenicillin β-sulphoxide methyl ester with Ac_2O to give the 2-*C*-β-acetoxymethylpenicillin derivative. We[2,3] later reported the rearrangement of phthalimidopenicillin α-sulphoxide with Ac_2O to give a mixture of 2-*C*-α- and -β-acetoxymethylpenicillins, isolated as the α-sulphoxides [(**1**) → (**2**) + (**3**)].

We now report the functionalization of both 2-*C*-methyl groups *via* multiple sulphoxide rearrangements with Ac_2O to give a new class of penicillins. Thus the Ac_2O rearrangement of (**2**) followed by silica gel chromatography gave (**4**)† in low yield (19%). The ring-expanded structure (**5**) was ruled out by its independent synthesis (95% yield) *via* the acetylation of (**6**)[2] with isopropenyl acetate,[4] followed by direct comparison. Subsequent oxidation of (**4**) with 1 equiv. of *m*-chloroperbenzoic acid (*m*-CPBA) gave the sulphoxide (**7**)† (84%). Treatment of (**7**) with Ac_2O followed by silica gel chromatography gave what we believe to be the triacetoxypenicillin (**8**)‡ (21%) as a mixture of isomers at 2-C in *ca.* 2:1 (isomer A:B) ratio: ν_{max} ($CHCl_3$) 1780 cm^{-1} (β-lactam), δ ($CDCl_3$) 2·05, 2·08, 2·19 (9-H, s each, OAc), 3·80 (s, CO_2Me, isomer A), 3·82 (s, CO_2Me, isomer B), 4·44, 4·66 (AB, *J* 12 Hz, CH_2OAc, isomer A), 4·68, 4·99 (AB, *J* 12 Hz, CH_2OAc, isomer B), 5·11 (3-H, isomer B), 5·20 (3-H, isomer A), 5·36, 5·76 (2d, *J* 4 Hz, 5-H, 6-H, isomer B), 5·65, 5·73 (2d, *J* 4 Hz, 5-H, 6-H, isomer A), 7·24 [s, $CH(OAc)_2$], and 7·86 (m, Ar).

Although similar multiple sulphoxide rearrangements on 2,2-dimethylthiochroman 1-oxide (**9**) provided (**10**), which could be hydrolysed to the formyl derivative, acid hydrolysis of (**8**) was not investigated due to the poor overall yield of (**8**) from phthalimidopenicillin (< 1%).



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† Structure assignment supported by i.r. and n.m.r. spectral data. For compound (**4**): ν_{max} ($CHCl_3$) 1778 cm^{-1} (β-lactam); δ($CDCl_3$) 2·03 and 2·13 (each 3H, s, OAc), 3·73 (3H, s, CO_2Me), 4·19 and 4·44, and 4·53 and 473 (each 2H, AB, *J* 12 Hz, CH_2OAc), 5·07 (1H, s, 3-H), 5·64 and 5·73 (each 1H, d, *J* 4 Hz), and 7·86 (4H, m).

‡ Attempts to oxidize (**5**) followed by a Pummerer rearrangement have not been successful.

[1] 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.

[2] D. O. Spry, *J. Amer. Chem. Soc.*, 1970, **92**, 5006.

[3] R. D. G. Cooper, L. D. Hatfield, and D. O. Spry, *Accounts Chem. Res.*, 1973, **6**, 32.

[4] G. E. Gutowske, B. J. Foster, C. J. Daniels, L. D. Hatfield, and J. W. Fisher, *Tetrahedron Letters*, 1971, 3433.