A Simple and Efficient Synthesis of the γ-Lactam Analogue of β-Lactam Antibiotics. Ring-expansion of Penicillins to Homopenicillins

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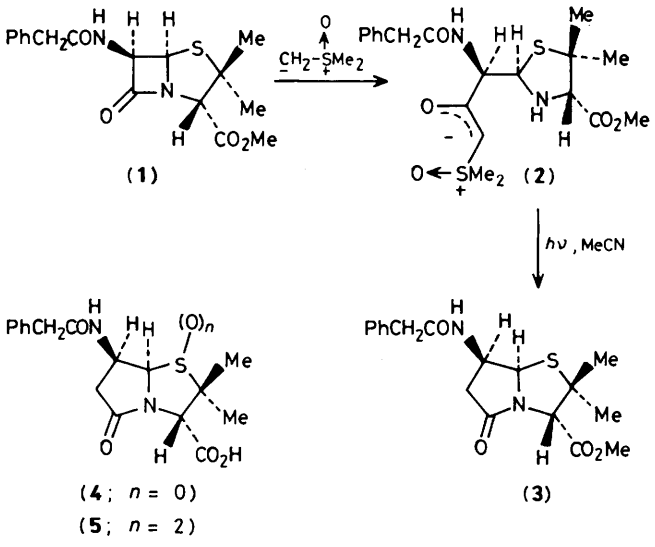
Irradiation of the β-ketosulphoxonium ylide (**2**), prepared easily from the benzylpenicillin methyl ester (**1**), with u.v. light results in the smooth formation of the corresponding homopenicillin methyl ester (**3**) which is hydrolysed to give benzylhomopenicillin (**4**) quantitatively.

Current attention is focused on the preparation of β-lactam analogues of β-lactam antibiotics because it has been recently documented that several of these compounds exhibit interesting antibacterial activity against a variety of Gram-positive and Gram-negative bacteria.[1]

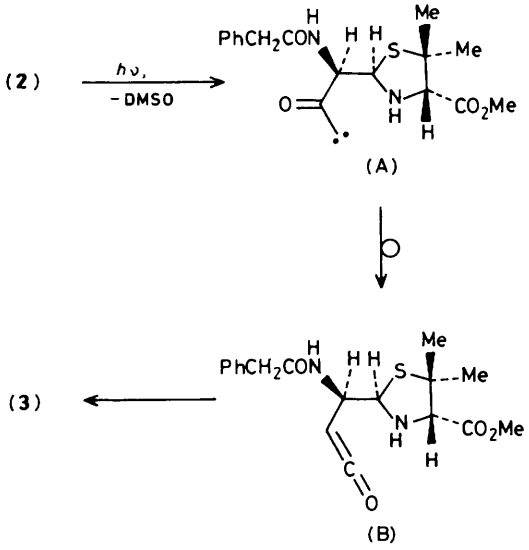
We describe here a simple and efficient synthesis of the benzylhomopenicillin (**4**),† a γ-lactam analogue of benzylpenicillin, which involves a new type of ring expansion of the β-lactam ring in penicillins,[3] in principle applicable to the preparation of the γ-lactam analogues of other β-lactam antibiotics. The special feature of this simple method is that all reactions proceed under mild conditions and the stereochemistry of the starting penicillins is retained in the resulting homopenicillins.

Benzylpenicillin methyl ester (**1**) (1.0 mmol) and trimethylsulphoxonium iodide (1.5 mmol) were added to a vigorously stirred mixture of 10 M-potassium hydroxide (2 ml) and methylene chloride (15 ml) at ambient temperature. After stirring for 3 h and chromatographic work up (silica gel, chloroform–methanol eluant) the mixture gave the corresponding β-ketosulphoxonium ylide‡ (**2**), m.p. 72—75 °C, in 90% yield. The structure of the ylide (**2**) was fully supported by microanalytical and spectral data.§

A solution of (**2**) (0.5 mmol) in dry acetonitrile was irradiated with a 160 W low-pressure mercury arc lamp under argon for 3 h, to give, after similar work up (eluant benzene–ethyl acetate), benzylhomopenicillin methyl ester (**3**), m.p. 81—83 °C, in 47% yield. Under thermal conditions, formation of (**3**) was not observed. The γ-lactam structure of (**3**)§ was confirmed unequivocally by its i.r. [$\nu_{max.}$ 1700 cm^{-1} (γ-lactam carbonyl)] and ^1H n.m.r. [δ 2.53 (1H, dd, *J* 1.7 and 17.5 Hz, 7β-H), 3.02 (1H, dd, *J* 7.3 and 17.5 Hz, 7α-H)] spectra. The relative configurations of (**3**) were established by



Scheme 1



Scheme 2. (DMSO = dimethyl sulphoxide)

† Phenoxymethylhomopenicillin has been already synthesised as a mixture of stereoisomers by H. H. Wasserman *et al. via* a multi-step process starting from diethyl formylsuccinate and D-penicillamine.[2]

‡ The formation of the β-ketosulphoxonium ylides has been observed in the reaction of carbonyl compounds such as lactones, imides, and α-lactams with dimethylsulphoxonium methylide.[4] However, there is no precedent for the formation of the β-ketosulphoxonium ylides starting from the β-lactam compounds. Employment of this method in cephalosporins gave a stereoisomeric mixture of the corresponding ylides.

§ All new compounds gave satisfactory microanalytical and spectral data consistent with their assigned structures.

Spectral data for (**2**): $C_{20}H_{28}N_2O_5S_2$; i.r.: $\nu_{max.}$ (KBr) 3300 (NH), 1740 (C=O), and 1660 (C=O); $\lambda_{max.}$ (MeCN) 255 (ε 1.1 × 10^4) and 205 nm (sh, 1.2 × 10^4); ^1H n.m.r. (270 MHz, $CDCl_3$): δ 1.17 (3H, s, 5-Me), 1.50 (3H, s, 5-Me), 3.34 (3H, s, SMe), 3.37 (3H, s, SMe), 3.53 (1H, s, 4-H), 3.61 (2H, s, CH_2Ph), 3.74 (3H, s, CO_2Me), 4.43 (1H, dd, *J* 6.0 and 8.5 Hz, 6-H), 4.64 (1H, s, COC*H*=SOMe$_2$), 5.00 (1H, d, *J* 6.0 Hz, 2-H), 6.41 (1H, d, *J* 8.5 Hz, D_2O-exchangeable NH), 7.27—7.37 (5H, m, Ph); *m/z* 440 (M^+).

Spectral data for (**3**): $C_{18}H_{22}N_2O_4S$, i.r. $\nu_{max.}$ (KBr) 3300 (NH), 1740 (C=O), 1700 (C=O), and 1660 cm^{-1} (C=O); $\lambda_{max.}$ (MeCN) 315 (ε 2 × 10^2), 299 (2 × 10^2), 258 (3 × 10^2), and 212 nm (6 × 10^3); ^1H n.m.r. (270 MHz, $CDCl_3$): δ 1.16 (3H, s, 2-Me), 1.40 (3H, s, 2-Me), 2.53 (1H, dd, *J* 1.7 and 17.5 Hz, 7β-H), 3.02 (1H, dd, *J* 7.3 and 17.5 Hz, 7α-H), 3.61 (2H, s, CH_2Ph), 3.75 (3H, s, CO_2Me), 4.51 (1H, s, 3-H), 4.57 (1H, m, 6-H), 5.80 (1H, d, *J* 5.9 Hz, 5-H), 6.18 (1H, d, *J* 4.7 Hz, D_2O-exchangeable NH), and 7.24—7.40 (5H, m, Ph); *m/z* 363 (M^+ + 1).

nuclear Overhauser effect difference spectra [selected details (270 MHz, $CDCl_3$, 27 °C): irradiation of 6α-H showed enhancements of 13% for 5α-H, 6% for 7α-H, and <2% for 7β-H]. Thus, the stereochemistry of (**3**) is consistent with that of penicillins (**1**).

Taking into consideration the known photochemical reactivity of sulphoxonium ylides,[5] a plausible mechanism for the formation of (**3**) from (**2**) is outlined in Scheme 2. The reaction is initiated by photolysis of (**2**) to generate a carbene (**A**) which undergoes Wolff rearrangement under the conditions employed to give a ketene intermediate (**B**). Subsequent intramolecular trapping of the ketene moiety by the thiazolidine ring-nitrogen in (**B**) affords the ultimate product (**3**).

Alkaline hydrolysis of (**3**) with 1 M-NaOH at ambient temperature gave the corresponding homopenicillin (**4**)§ without cleavage of the γ-lactam ring. Oxidation of (**4**) with excess of hydrogen peroxide gave the corresponding sulphone (**5**) [m.p. 84—86 °C, $\nu_{max.}$ 1730 cm^{-1} (γ-lactam carbonyl)],§ quantitatively. Unlike (**4**), the γ-lactam ring of (**5**) is highly sensitive to alkaline hydrolysis. The sulphone (**5**), however, did not show appreciable antibacterial activity or β-lactamase inhibition.

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