A New Rearrangement of a 4-Mercaptoazetidin-2-one *via* a Thioaldehyde Intermediate

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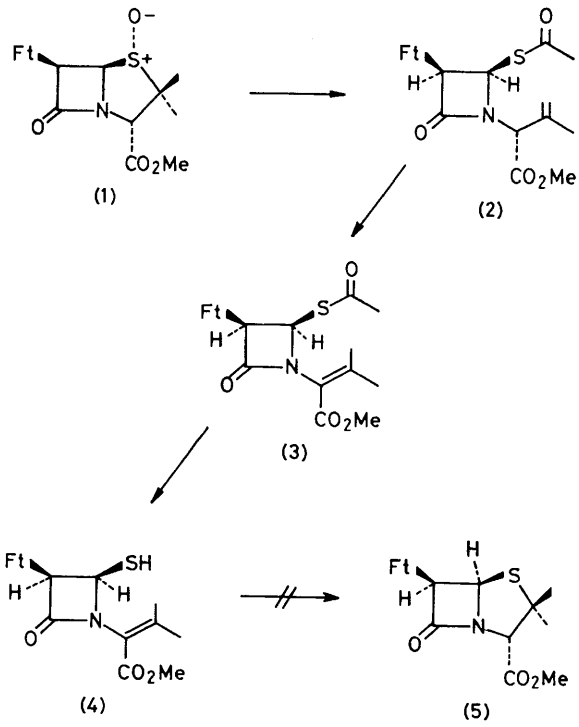
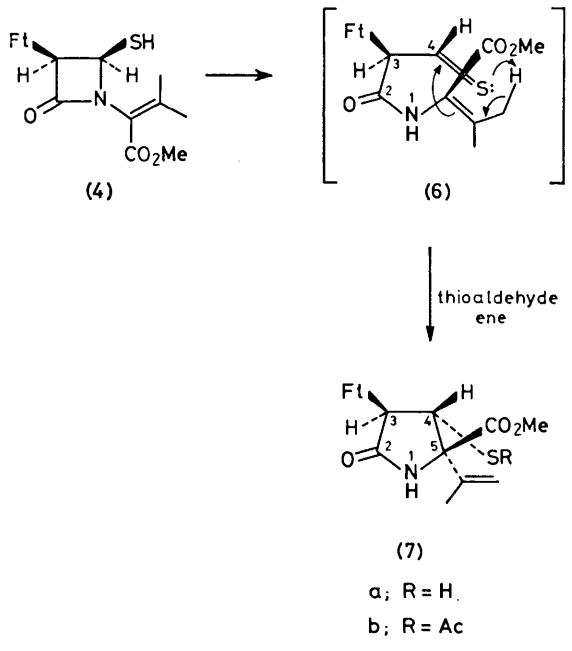
Summary The 4-mercaptoazetidin-2-one (**4**) was prepared by a short and efficient route from phthalimidopenicillin methyl ester, and its pyrolysis provided a new γ-lactam (**7a**) stereospecifically *via* an ene reaction of a thioaldehyde.

DURING the course of studies on the biomimetic synthesis of penicillins we wished to examine the Michael closure of mercaptoazetidinones, such as (**4**), which was invoked in an early biosynthetic scheme for these substances.[1,2] To provide a suitable substrate for these studies we converted the sulphoxide (**1**) of methyl phthalimidopenicillinate, *via* the *seco*-thioester (**2**) (80%, acetic anhydride, trimethyl phosphite) into the conjugated derivative (**3**) (65%, triethylamine in $CHCl_3$, m.p. 210—211 °C).[3] Deprotection of the thioester (**3**) was achieved by sequential treatment with mercury(II) acetate (1 equiv., acetic acid) and then reductive cleavage of the mercury derivative (hydrogen sulphide in CH_2Cl_2) to yield (**4**) [61%, m.p. 176 °C (decomp.)].[4] All our attempts to effect ring closure of (**4**) to the known phthalimidopenicillin methyl ester (**5**), under acidic, basic, or free radical (azobis-isobutyronitrile) conditions have failed (limit of detection *ca.* 0·1%). The penicillin (**5**) was shown to be stable under all reaction conditions tested. However in the course of these experiments we uncovered an interesting reaction of this mercaptan (**4**) as follows. On pyrolysis (176 °C, under N_2, 10 min) it was cleanly converted into the γ-lactam (**7a**) [60%, m.p. 204—208 °C, i.r. ($CHCl_3$):



SCHEME 1. Ft = phthalmido.



SCHEME 2

3400, 1700, 1730, and 1720 cm^{-1}; ^1H n.m.r. ($CDCl_3$, 300 MHz): δ 1·91 (d, J 9 Hz, 1H, SH), 1·96 (s, 3H, vinyl-Me), 3·87 (s, 3H, ester Me), 4·49 (dd, J 11 and 9 Hz, 1H, 4-H, *trans*), 4·74 (d, J 11 Hz, 1H, 3-H), 5·36 (m, 2H, $=CH_2$), 6·44 (br s, 1H, NH), and 7·79 (m, 4H, ArH); addition of D_2O led to deuterium exchange of the peaks at δ 1·91 and 6·44, while the dd at δ 4·49 collapsed to a broadened d, J 11 Hz; m.s. (70 eV), *m/e* 360 (M^+)]. Acetylation of (**7a**) (acetyl bromide, 25 °C) gave the ester (**7b**) [98%, m.p. 247—249 °C, i.r. ($CHCl_3$): 3400, 1770, and 1720 cm^{-1}; ^1H n.m.r. ($CHCl_3$): δ 1·93 (s, 3H, vinyl-Me), 2·35 (s, 3H, CH_3COS), 3·85 (s, 3H, CO_2CH_3), 5·02 (m, 4H, $=CH_2$, 3- and 4-H), 6·62 (br s, 1H, NH), and 7·75 (m, 4H, ArH); m.s. (70 eV), *m/e* 402 (M^+)]. The stereochemistry at C-4 and C-5 in these products was determined by a nuclear Overhauser effect (n.O.e.) on 3-H (+13%) on irradiation of the vinyl methyl. There was no n.O.e. on 4-H under these conditions. We rationalize this result as depicted in Scheme 2. Thus preliminary thermal opening of (**4**) to the thioaldehyde (**6**) provides an intermediate which by an 'ene' type reaction directly yields the γ-lactam (**7a**).[5] The stereochemical outcome is presumably the result of the directing effect of the C-3 phthalimido substituent.

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[1] H. V. R. Arnstein and J. C. Crawhall, *Biochem. J.*, 1957, **67**, 180. However tracer experiments have disproved the *in vivo* validity of this suggestion: *cf.* P. A. Fawcett, J. J. Usher, J. A. Huddleston, R. C. Bleaney, J. J. Nisbet, and E. P. Abraham, *Biochem. J.*, 1976, **157**, 651.

[2] The realization of this Michael reaction from phthalimidoanhydropenicillin has been claimed: *cf.* S. Wolfe, R. N. Bassett, S. M. Caldwall, and F. I. Wasson, *J. Am. Chem. Soc.*, 1969, **91**, 7205.

[3] L. D. Hatfield, J. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Lett.*, 1970, 4897.

[4] Similar mercaptoazetidinones have been made by other procedures: *cf.* R. Lattrell, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 925; M. D. Bachi and O. Goldberg, *J. Chem. Soc., Perkin Trans.* 1, 1974, 1184; J. E. Baldwin and M. Christie, *J. Chem. Soc., Chem. Commun.*, 1978, 239; M. Narisada, H. Onoue, M. Ohtani, F. Watanabe, T. Okada, and W. Nagata, *Tetrahedron Lett.*, 1978, 1755; T. E. Gunda, I. Lakatos, E. R. Farkas, J. Cs. Jászberényi, J. Tamás, and M. Mák, *ibid.*, 1979, 2929.

[5] A similar γ-lactam was obtained by direct base-catalysed rearrangement of penicillin sulphoxides: *cf.* J. E. Baldwin, S. R. Herchen, G. Schulz, C. P. Falshaw, and T. J. King, *J. Am. Chem. Soc.*, 1980, **102**, 7815.