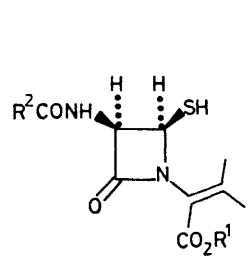
Preparation of a Penicillin-derived 4-Mercaptoazetidin-2-one

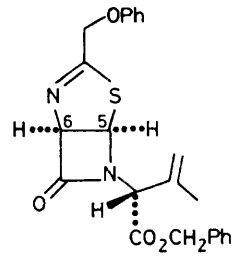
By JACK E. BALDWIN* and MICHAEL A. CHRISTIE
(*Chemistry Department, Massachusetts Institute of Technology, Cambridge, Massachusetts* 02139)

Summary The 4-mercaptoazetidin-2-one (**3a**) was prepared by acid treatment of the penicillin-derived β-lactam (**2**); thermolysis of (**3a**) gave the thiazole (**4**), by a process which did not proceed *via* the thiazoline (**2**).

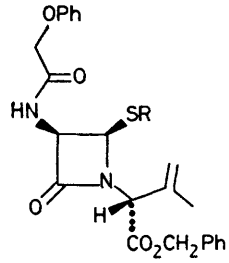
MERCAPTOAZETIDINONES (1,2-secopenicillins) of general structure (**1**) have been proposed in early studies on penicillin biosynthesis as intermediates on the path to penicillins[1] and more recently they have been implicated in the conversion of anhydropenicillin into penicillins.[2] Preparations of these compounds have involved total synthesis[3—5] and reduction of sulphenic acids derived from penicillin sulphoxides,[6] under which conditions they close spontaneously to thiazolines, *e.g.* (**2**), unless intercepted by acylating agents.[7] Other reports of their transient preparation involve treatment of penicillins with strong bases,[8] wherein they were trapped by alkylation[8,9] and recently it was claimed[10] that such thiols can be obtained by reaction of the thiazolines (**2**) sequentially with silver perchlorate and hydrogen sulphide. In addition, such thiols have been freed from the thiazolines (**2**) with acid and trapped[11] by alkylation, halogenation, or by reaction with sulphenyl halides. We report a simple and efficient preparation of an example of this class from the thiazoline (**2**).



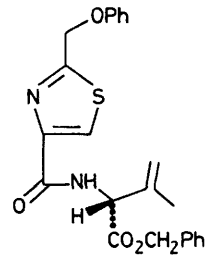
(1)



(2)



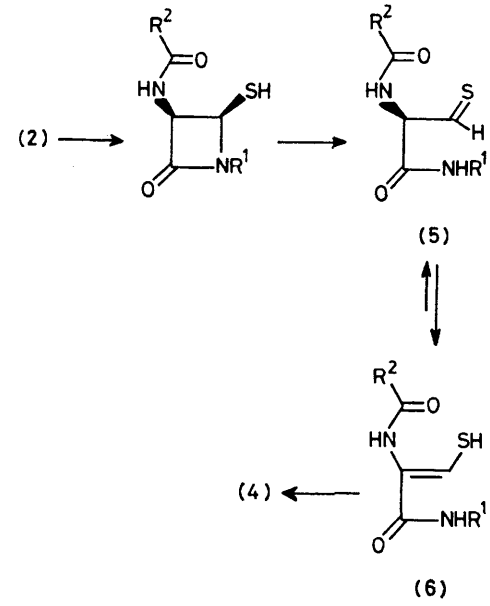
(3) a: R = H
b: R = ⟩
c: R = COMe



(4)

Thus on warming (**2**) in 1 M aqueous hydrochloric acid–methanol (1:3) at 35—40 °C for 10 min, the thiol (**3a**)† precipitated (93%) and was recrystallized (CH_2Cl_2–Et_2O) to m.p. 122—125 °C, n.m.r. ($CDCl_3$) δ 1·88 (s, 3H), 2·02 (d, *J* 8 Hz, 1H), 4·51 (s, 2H), 4·82 (s, 1H), 4·90—5·15 (m, 2H), 5·17 (s, 2H), 5·30—5·60 (m, 2H), 6·77—7·40 (m, 10H), and 7·69 (d, *J* 8·Hz, 1H); i.r. ($CHCl_3$) 3410, 1770, 1740, and 1683 cm^{-1}. On refluxing the thiol (**3a**) in the above solvent mixture it was quantitatively transformed to the known thiazole (**4**).[6] The structure of (**3a**) was substantiated by oxidation (I_2, tetrahydrofuran, $NaHCO_3$) to the disulphide (**3b**) [oil, 65%; n.m.r. ($CDCl_3$) δ 1·87 (s, 3H), 4·50 (s, 2H), 4·87 (s, 1H), 4·97—5·36 (m, 6H), and 6·76—7·58 (m, 11H); i.r. ($CHCl_3$) 3400, 1770, 1740, and 1685 cm^{-1}], and by acetylation (acetyl chloride–pyridine, −10 °C, 20 min) to the acetate (**3c**) [oil, 63%; n.m.r. ($CDCl_3$) δ 1·84 (s, 3H), 2·20 (s, 3H), 4·50 (s, 2H), 4·77—5·10 (m, 3H), 5·18 (s, 2H), 5·46 (dd, *J* 5 and 8 Hz, 1H), 5·94 (d, *J* 5 Hz, 1H), and 6·77—7·43 (m, 11H); i.r. ($CHCl_3$) 3400, 1775, 1740, 1703, and 1690 cm^{-1}]. This substance (**3c**) was identical (i.r., n.m.r.) to a sample prepared directly from penicillin V sulphoxide benzyl ester by thermolysis in the presence of trimethyl phosphite–acetic anhydride.[7]

It was of interest to observe that the thiol (**3a**) on heating (140 °C) was converted quantitatively into the thiazole (**4**), under conditions in which the thiazoline (**2**) was recovered unchanged, thereby proving that the thiazoline is not an intermediate.[12] A reasonable alternative is that preliminary opening of the β-lactam provides the thioaldehyde (**5**) which as its enol (**6**) closes to the thiazole (**4**) (Scheme). A



SCHEME.

similar mechanism could hold for the acid-catalysed conversion of (**2**) into (**4**), since we have now shown that the thiol (**3a**) is an intermediate by its isolation. It is interesting that the more obvious direct conversion of (**2**) into (**4**) implies the breakage of two mutually orthogonal bonds, *i.e.*, C(6)–H and C(5)–N.

We thank the National Science Foundation, National Institutes of Health for financial support, and members of the Lilly Research Laboratories for helpful discussions.

(*Received*, 18*th November* 1977; *Com.* 1193.)

† All new compounds gave satisfactory analytical data.

[1] H. R. V. Arnstein and J. C. Crawhill, *Biochem. J.*, 1957, **67**, 180.
[2] S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. J. Wasson, *J. Amer. Chem. Soc.*, 1969, **91**, 7205.
[3] R. Lattrell, *Angew. Chem. Internat. Edn.*, 1973, **12**, 925.
[4] M. D. Bachi and O. Goldberg, *J.C.S. Perkin I*, 1974, 1184.
[5] J. E. Baldwin and P. Singh, unpublished work.
[6] R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.
[7] L. D. Hatfield, J. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Letters*, 1970 4897.
[8] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Tolliday, *Chem. Comm.*, 1971, 590.
[9] M. A. Harris, I. McMillan, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, and R. Southgate, *J.C.S. Chem. Comm.*, 1973, 57.
[10] Y. Hamashima, K. Ishikura, H. Ishitobi, H. Itani, T. Kubota, K. Minami, M. Murakami, W. Nagata, M. Narisada, Y. Nishitani, T. Okada, H. Onoue, H. Satoh, Y. Sendo, T. Tsuji, and M. Yoshioka, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics,' ed. J. Elks, Special Publication No. 28, The Chemical Society, London, 1977, p. 245. Dr. M. Narisada has since informed us of his own independent observation of the acid-catalysed ring opening of thiazolines, such as (**2**).
[11] A. G. Long in Ref. 10, p. 214.
[12] We thank Mr. Mankil Jung for this experiment.