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BASE-INDUCED TRANSFORMATIONS OF AZETIDIN-2-ONE-4-DISULPHIDES

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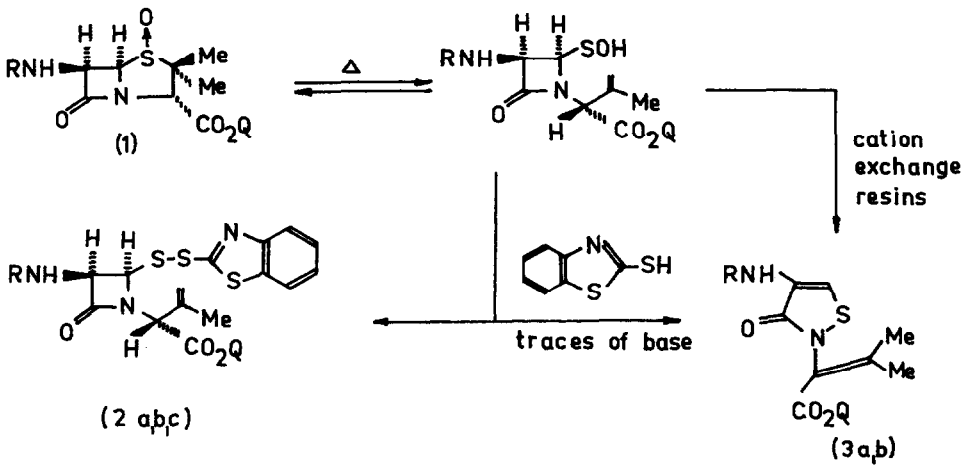
One of the methods used for trapping the sulphenic acids, derived from penicillin sulphoxides, has been the reaction with thiols[1,2]. Transformation of derivatives of this type (2)[2] formed with 2-mercaptobenzthiazole gave rise to the formation of 2-halomethyl-2-methylpenams and 3-halocephams[2,3].

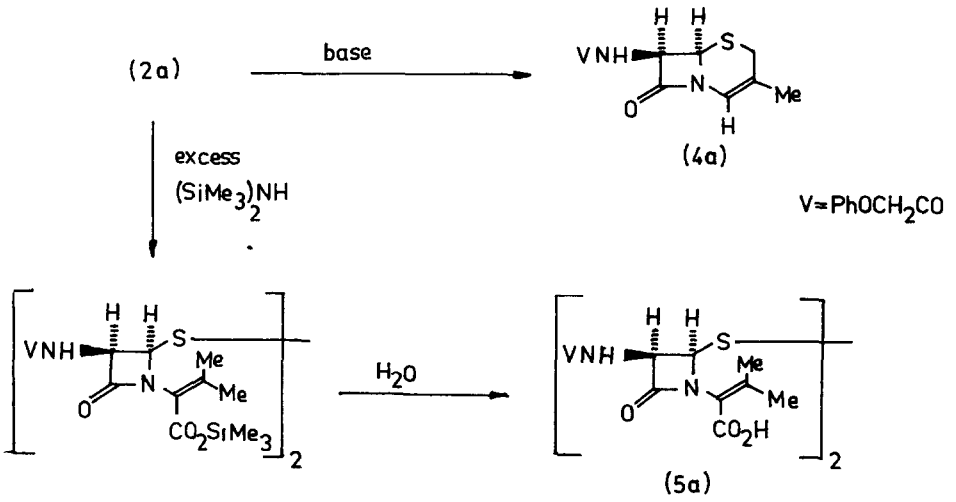


Further study of the transformation of the benzthiazole derivatives (2) has shown that the substituent on the β-lactam nitrogen plays an important role on the course of the reaction.

Sulphoxides of penicillin G (1; R = $PhCH_2CO$, Q = H) or penicillin V (1; R = $PhOCH_2CO$, Q = H) reacted with 2-mercaptobenzthiazole forming the disulphide (2a,b). (1c) (R = $PhCH_2CO$, Q = TCE) gave (2c) in a similar reaction[2]. In the presence of traces of base, however, penicillin sulphoxide esters gave the isothiazolone derivatives (3a) (R = $PhCH_2CO$, Q = CH_2OAc, m.p. 156-8 °C) and (3b) (R = $PhCH_2CO$, Q = TCE, m.p. 212-3 °C/[4]. These compounds were also obtained in 70-80 % yield from the corresponding penicillin sulphoxide esters upon heating in dioxane in the

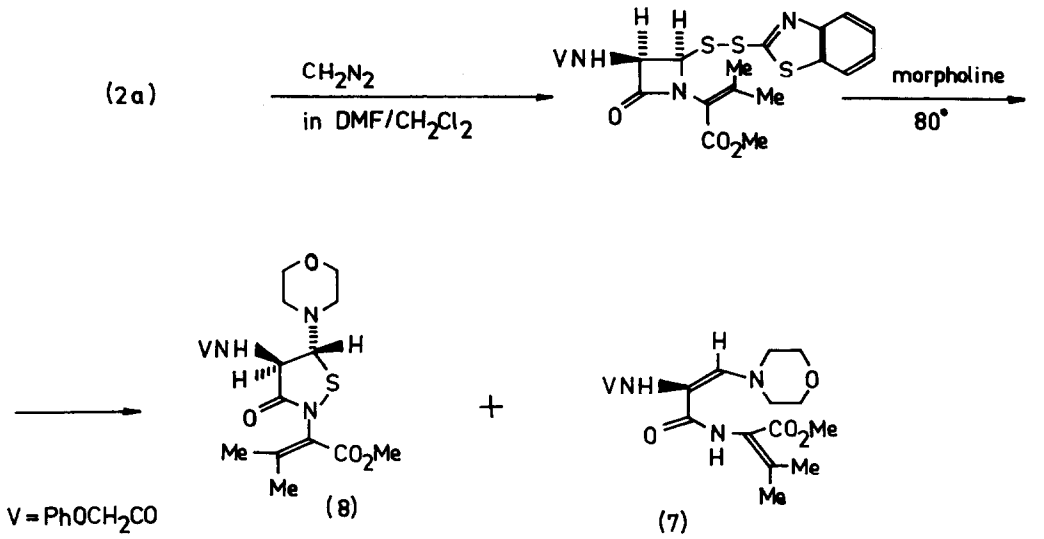
presence of cation exchange resins[5a], and by other methods[5b].

Reaction of (2a) (R = $PhOCH_2CO$) with $NaBH(OMe)_3$ or Zn/H^+ resulted in the formation of the decarboxylated derivative (4a) in an almost quantitative yield. The same transformation took place if the disulphide (2a) was kept in the presence of base (triethylamine or morpholine) at 20°.



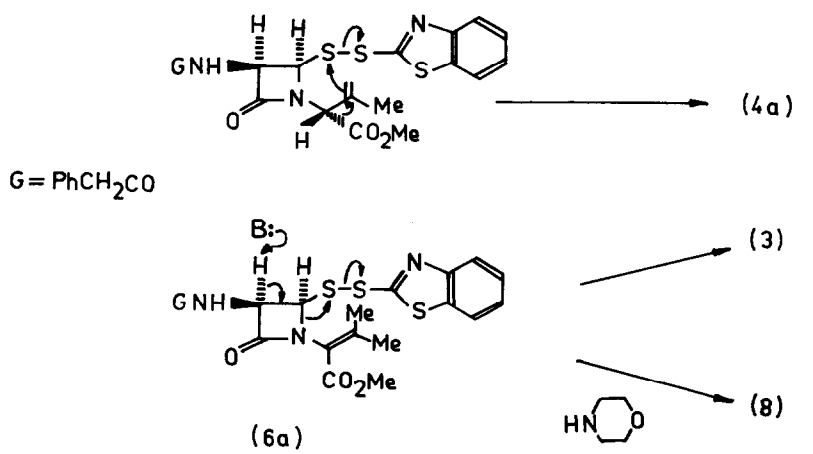
Treatment with excess hexamethyldisilazane, however, gave the disulphide (5a) which has been obtained previously by other methods.

Diazomethane transformed (2a) in dimethylformamide / methylene chloride solution to the methyl ester (6a) which when heated in dimethoxymethane in the presence of morpholine gave (7) and (8) in the ratio of 8:1 with the following characteristics: (7):m.p. 187-8°, ν_{max}(KBr) 1717, 1661, 1592, 1490, 1232 cm^{-1}, δ (90 MHz, CD_2Cl_2, TMS) 1,74 (s, 3H), 2.06 (s, 3H), 3.30-3.42 and 3.58-3.68 (m, 8H), 3,67 (s, 3H), 4.65 (s, 2H), 6.62 (broad s, 1H), 6.94-7.44 (m, 5H), 7.33 (s, 1H), 7.54 (broad s, 1H), mass: 417 (M^+), λ_{max} (dioxan): 224 and 284 nm, in accordance with the values published for similar compounds[7]. (8): m.p.: 156°, ν_{max} (KBr) 1699, 1635, 1215 cm^{-1}, δ (100 MHz, DMSO-d_6, TMS) 1.88 (s, 3H), 2.11 (s, 3H), 2.85-3.05 and 3.55-3.75 (m, 8H), 3.52 (s, 3H), 4.12 (d, 1H, J = 4Hz), 4.58 (s, 2H), 4.88 (dd, 1H, J_1 = 8Hz, J_2 = 4Hz), 6.4-7.1 (m, 5H), 8.62 (d, 1H, J = 8Hz).



In the case of formation of (4a) the corresponding disulphide (2a) undergoes a decarboxylation process. A similar reaction was observed in the ring enlargement of phenoxymethylpenicillin sulphoxide by Morin and Cooper[5c].

In the reaction of the disulphide (6a) a similar process is not possible; (8) is formed in a rearrangement, similar to the selective transformation of (1) to (3) upon treatment with cation exchange resins.



The previously suggested β-elimination[5b] takes place in the reaction giving rise to the formation of (7), after substitution at C-4.

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