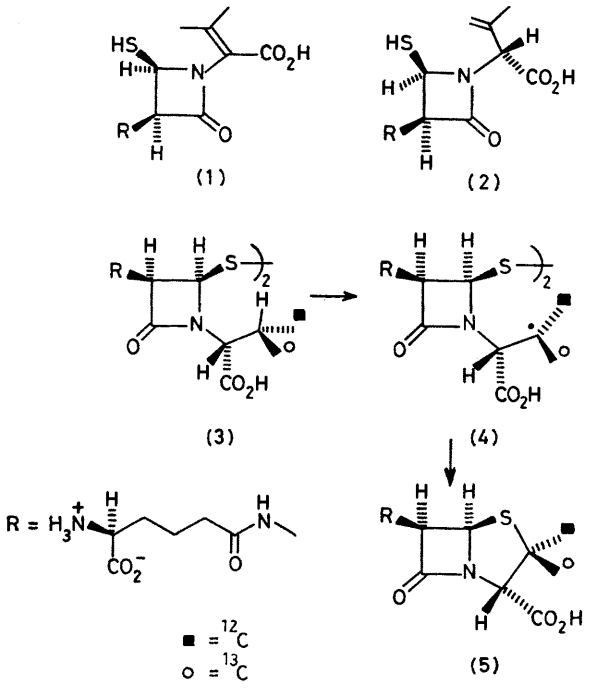
Penicillin Biosynthesis. A Model for Carbon–Sulphur Bond Formation

By JACK E. BALDWIN* and TERENCE S. WAN
(*Dyson Perrins Laboratory, South Parks Road, Oxford* OX1 3QY)

Summary Oxidative decarboxylation of bis(4-carboxy-4,4-dimethylbutyl) disulphide yields 2,2-dimethyltetrahydrothiophen; this experiment is presented as a chemical model for the biosynthesis of the carbon–sulphur [C(2)—S(1)] bond of penicillins.

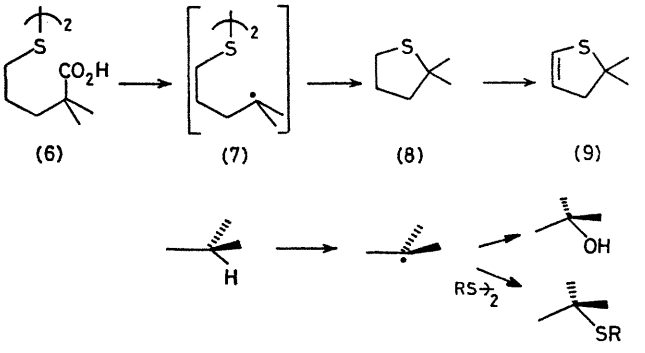
IN spite of much effort, details of the nuclear biosynthesis of penicillins–cephalosporins remain obscure.[1] However, the incorporation of L-α-aminoadipyl-L-cysteinyl-D-[2-^{3}H]-valine into penicillin N, by an extract of *Cephalosporium-acremonium*,[2] suggests that dehydropeptides, such as (**1**) or (**2**), are not involved contrary to earlier speculations.[3] Furthermore, the incorporation of [$^2H_6$]valine into penicillin N with retention of all six deuterons,[4] and the retention of valine C(3) stereochemistry,[5] strongly limits the type of biomechanism for formation of the carbon–sulphur bond. We suggest a pathway which is in accord with these restrictions and is supported by *in vitro* experiments.



SCHEME 1

It seemed reasonable that dehydrogenation of the peptide (**3**) to the carbon radical (**4**) would result in intramolecular trapping by the disulphide linkage to yield the cyclised peptide (**5**) (Scheme 1). Provided that intramolecular trapping were faster than rotation in the radical (**4**) then this mechanism agrees with all known facts.

To evaluate the chemical feasibility of this mechanism, a model system was examined. Thus the disulphide (**6**), m.p. 54—55 °C, was prepared from isobutyric acid by sequential allylation (lithium di-isopropylamide, allyl bromide), anti-Markownikoff hydrobromination, thiourea displacement, followed by hydrolysis (NaOH) and oxidative coupling (I_2). Oxidative decarboxylation of (**6**) [$Pb(OAc)_4$, tetrahydrofuran, 25 °C, 2 h] gave 2,2-dimethyltetrahydrothiophen (**8**) [27%, m.p. ($HgCl_2$ complex)[6] 131—132 °C] and 2,2-dimethyl-2,3-dihydrothiophen (**9**) [15%, oil; δ ($CDCl_3$) 1·50 (s, 6H), 2·5 (m, 2H), 5·4 (m, 1H), and 6·1 (br d, *J* 6 Hz, 1H)], separated by preparative g.l.c. (10% SE-30/Chrom. P.). The most reasonable interpretation of these observations is that the carbon radical (**7**), produced by oxidative decarboxylation of (**6**), is intercepted by the disulphide to yield (**8**), which is subsequently partially converted into (**9**), a reaction with ample precedence.[7] A recent preparative observation by Maki and Sako,[8] within a penicillin system, adds further support to the chemical basis of our hypothesis.



SCHEME 2

It might be reasonably asked what source of the carbon radical (**4**) might exist in the cell. One intriguing possibility derives from observations which suggest that the mechanism of hydroxylation enzymes has characteristics in accordance with carbon radical intermediates,[9] which are normally converted into alcohols. However the close location of a disulphide might yield the corresponding sulphide, as a diversion of the normal pathway (Scheme 2).

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