Tetrahedron Letters,Vol.26,No.34,pp 4107-4110,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

β-LACTAMS FROM TETRAHYDRO-1,2-OXAZINE-3,6-DIONES

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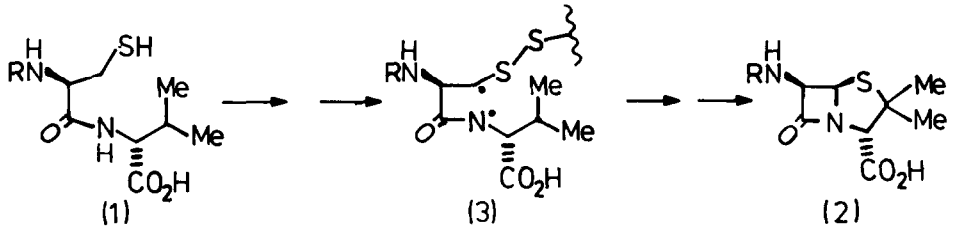
SUMMARY: The photolysis and thermolysis of (4) and the photolysis of (5) result in the formation of the β-lactams (6) and (7); a mechanism which involves 1,4-diradicals is proposed and the possible relationship of this process to the biosynthesis of the β-lactam ring of isopenicillin N is discussed.

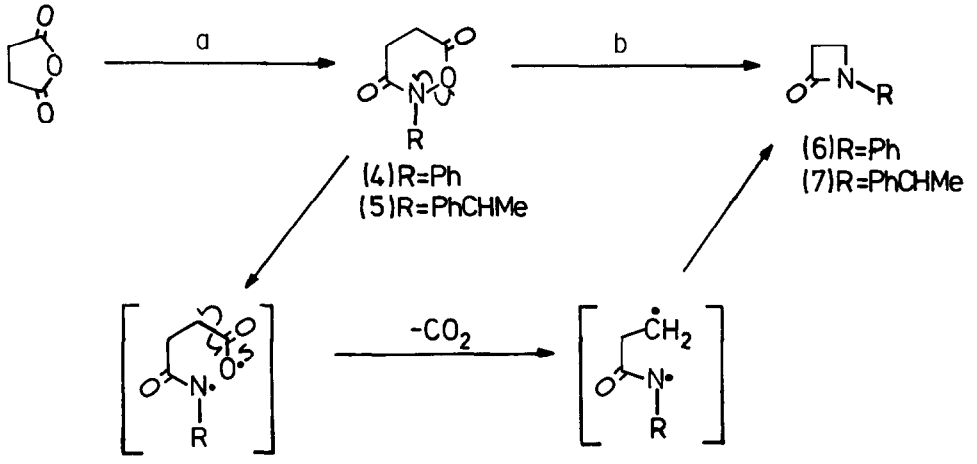
It has been suggested that the enzymic conversion of the tripeptide (1) into isopenicillin N (2) might involve radicals[1,2,3] and this has led to the development of an *in vitro* model system for the oxidative cyclisation of a simple amide to a β-lactam.[2] We were interested in the possibility that an enzyme-bound 1,4-diradical such as (3) could be a plausible intermediate on the biosynthetic pathway to isopenicillin N.[4] In this communication we describe the preparation of two simple β-lactams using a reaction based on this speculation, and outline a scheme for the biosynthesis of isopenicillin N which involves only radical intermediates.



We reasoned that the thermolysis or photolysis of N-substituted tetrahydro-1,2-oxazine-3,6-diones such as (4) should cause homolytic cleavage of the weak N-O bond followed by rapid decarboxylation.[5] The collapse of the resulting 1,4-diradical to a β-lactam[6] would serve as a simple chemical model for the suggested intermediacy of such radicals in the biosynthesis of isopenicillin N.

The precursors (4) and (5) were prepared by the reaction of the appropriate hydroxyl-

amine with succinic anhydride followed by dehydration with dicyclohexylcarbodiimide.[7,8] The precursor (4) was thermolysed under nitrogen by placing it in a flask and immersing this for one minute in a bath preheated to 190°.[9] The β-lactam (6), whose structure was confirmed both by spectroscopic techniques and by correlation with an authentic sample,[10] was isolated in ca. 16% yield after chromatography. A higher yield (20%) of this β-lactam was obtained on photolysis of (4) in benzene (40 mins., 450W medium pressure Hg lamp), in both the photolysis and the thermolysis of (4) the β-lactam was the only discrete product isolated. In a similar manner the photolysis of (5) (220hr., C_6H_6, 4W low pressure Hg lamp, 21%) gave the corresponding β-lactam (7). This shows that direct conjugation of the nitrogen atom with an aromatic ring is not a pre-requisite for the formation of β-lactams using this reaction.



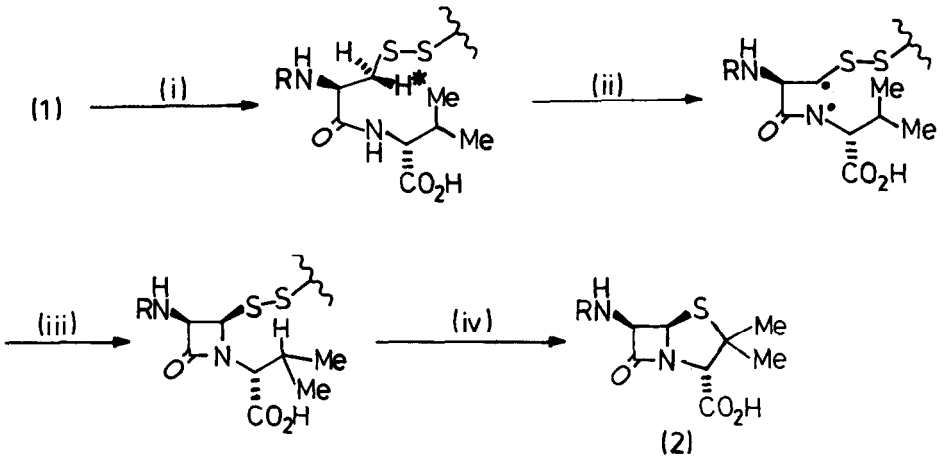
a) (i) RNHOH; (ii) DCC (43-55%): b) hν or 190° (see text for yields).

The possibility that the β-lactams were formed *via* the intermediacy of the corresponding acrylic amides was ruled out since neither the photolysis nor the thermolysis of these compounds gave β-lactams under the conditions used for the reactions of (4) and (5).

We propose that these results are best accounted for in terms of 1,4-diradicals as outlined above, and that this explanation is consistent with the suggested involvement of such species in the biosynthesis of isopenicillin N. We suggest a scheme for the enzymic conversion of the tripeptide (1) (Scheme 1) into isopenicillin N which incorporates this speculation into the scheme which has recently been proposed by Baldwin, based on model

reactions and extensive enzymic investigations.[11]

Scheme 1. Hypothetical Scheme for Biosynthesis of Isopenicillin N.[11,12]



(i) Covalent binding of (1) to penicillin synthetase (= HS~) via disulphide link.[4]

(ii) Stereospecific removal of H* by oxidation.

(iii) Formation of 4-membered ring with retention of configuration about the new bond by rapid collapse of the 1,4-diradical.[13]

(iv) A detailed mechanism for this conversion has been proposed recently by Baldwin.[11]

We thank Professor J.E. Baldwin and Dr. A.H. Davidson for discussions relating to this work, and the S.E.R.C. for a postgraduate assistantship (to J.N.).

References

1. J.E. Baldwin, A.L.J. Beckwith, A.P. Davis, G. Procter and K.A. Singleton, Tetrahedron, 1981, 37, 2181.

2. J.E. Baldwin and A.P. Davis, J. Chem. Soc., Chem. Commun., 1981, 1219; J.E. Baldwin, A.P. Davis and L.D. Field, Tetrahedron, 1982, 38, 2777.

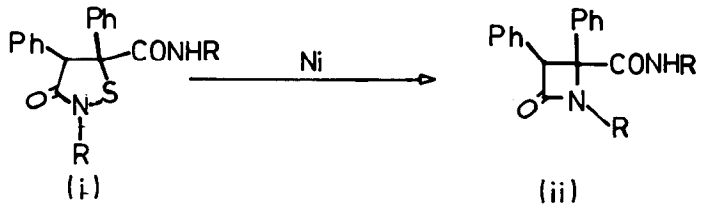
3. An alternative mechanism involving ionic intermediates was proposed recently; C.J. Easton, J. Chem. Soc., Chem. Commun., 1983, 1349.

4. The thiol group is almost certainly involved in the binding of (1) to the enzyme; R.M. Adlington, R.T. Aplin, J.E. Baldwin, B. Chakravarti, L.D. Field, E.-M. John,

E.P. Abraham and R.L. White, Tetrahedron, 1983, 39, 1061.

5. The acetoxyl radical has a half-life of ca. 4 x 10^{-8} s with respect to decomposition into CO_2 and $CH_3^{\bullet}$, P.S. Skell and D.D. May, J. Amer. Chem. Soc., 1981, 103, 967.

6. It has been suggested that the formation of β-lactams (i) in the desulphurisation of (ii) might involve 1,4 diradicals, although in this case there is the possibility that the reaction takes place via organo-nickel species; T. Minami and T. Agawa, J. Org. Chem., 1974, 39, 1210.



(i) (ii)

7. All new compounds were characterised by microanalysis, n.m.r., i.r. and m.s. measurements.

8. P. Gygax and A. Eschenmoser, Helvetica Chimica Acta, 1977, 60, 507.

9. These precise conditions are important for the thermal β-lactam-forming reaction.

10. Prepared by the cyclisation of N-phenyl-3-bromoproprionamide.

11. For an excellent account of recent advances in this area and extensive discussion on the nature of the enzymic reactions see, J.E. Baldwin, "Recent Advances in the Chemistry of β-Lactam Antibiotics", pp. 62-85, Eds. A.G. Brown and S.M. Roberts, R.S.C. Special Publication No. 52, 1985.

12. For a related scheme involving the proposed intermediacy of a radical α- to sulphur, see A.L.J. Beckwith and C.J. Eaton, Tetrahedron, 1983, 39, 3995.

13. The formation of cyclobutanes via the cyclisation of 1,4-diradicals takes place with retention of configuration; P.G. Schultz and P.B. Dervan, J. Amer. Chem. Soc., 1982, 104, 6660.

(Received in UK 15 May 1985)