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β-Lactams from Tetrahydro-1,2-oxazine-3,6-diones, and a Labelling Study of the Product Stereochemistry

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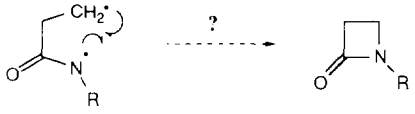
Dedicated to Emeritus Professor Hans Suschitzky, University of Salford, on the occasion of his 80th Birthday

Abstract: The stereochemistry of the N–C bond-forming step in the photochemical conversion of a tetrahydro-1,2-oxazine-3,6-dione to a β-lactam has been shown to take place with scrambling of stereochemistry using a deuterium labelled precursor.

The β-lactam ring system has been, and continues to be, an object of interest from both a synthetic and biosynthetic point of view.[1] Following a simplistic biosynthetic speculation, we designed a reaction which was based on the idea that a diradical such as **1** might undergo collapse to a β-lactam (Scheme 1).[2] In this paper we report the details of this work, a subsequent investigation into the stereochemistry of the bond-forming step using stereospecifically labelled precursor, and the isolation of a β-lactam from thermolysis of a tetrahydro-1,2-oxazine-3,6-dione.



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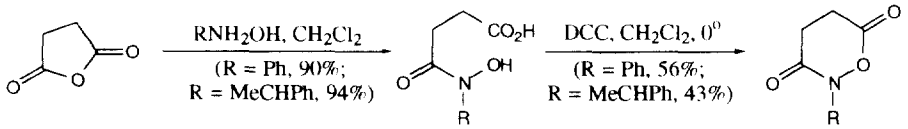
Scheme 1

Two representative tetrahydro-1,2-oxazine-3,6-diones **2** and **3** were prepared by reaction of maleic anhydride and the appropriate *N*-substituted hydroxylamine to give the *N*-hydroxysuccinamic acids, which were then closed by treatment with dicyclohexylcarbodiimide (DCC) (Scheme 2).

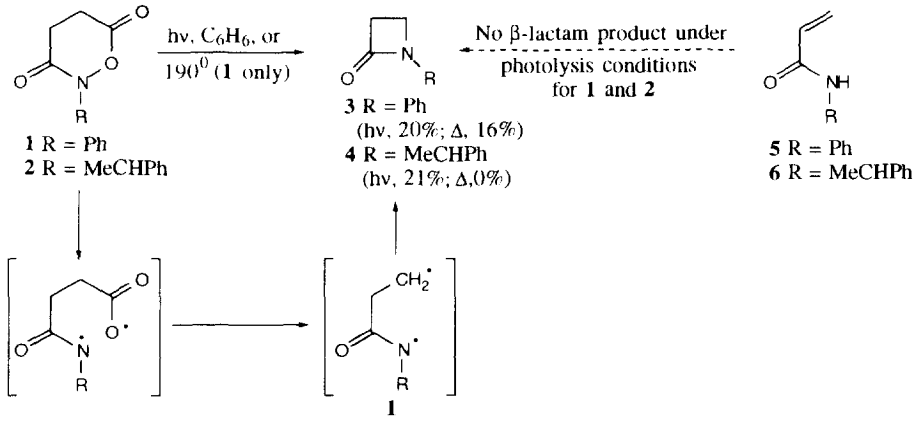
The tetrahydro-1,2-oxazine-3,6-dione system was chosen as a potential precursor of the desired diradical on the reasoning that the weak N–O bond should be cleaved homolytically under the appropriate photolysis or thermolysis conditions. The resulting diradical should undergo decarboxylation to provide the immediate diradical precursor to the β-lactam (Scheme 3). Thermolysis of the *N*-phenyl substrate **2** at 190° provided a



1 R = Ph
2 R = MeCHPh

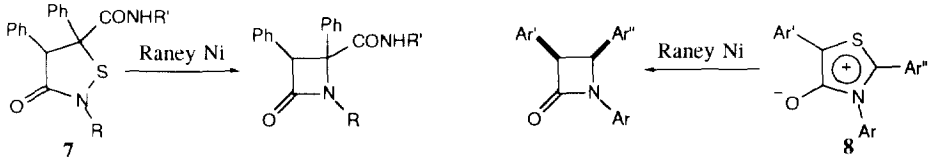
Scheme 2

complex mixture from which the desired β-lactam **4** was isolated as the only discrete product. Photolysis of this precursor also provided β-lactam **4** in slightly higher yield and again this was the only identifiable product which could be isolated. Photolysis of tetrahydro-1,2-oxazine-3,6-dione **3** also gave the corresponding β-lactam **5** in similar yield (Scheme 3). An alternative mechanism which could lead in principle to β-lactams would involve the intermediacy of the acrylamides **5** and **6**, as acrylamides have been reported to undergo this type of photochemical ring closure.[3] These acrylamides were prepared[4] and exposed to the photochemical conditions which produce β-lactams from tetrahydro-1,2-oxazine-3,6-diones **1** and **2** but no β-lactams could be detected by ir and ^{1}H nmr spectroscopy, making these acrylamides unlikely intermediates. The simplest rationalisation of these results would seem to be that anticipated (*vide supra*), which involves the intermediacy of diradicals.



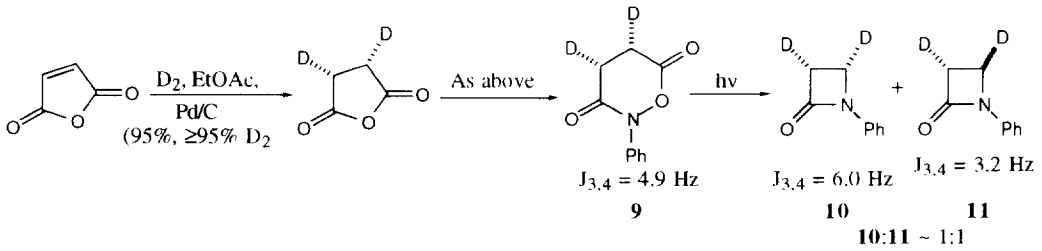
Scheme 3

The intermediacy of diradicals analogous to **1** has been suggested in the formation of β-lactams in the Raney nickel desulphurization of **7** (Scheme 4),[5] but in this case the possibility of the intermediacy of organonickel species is also a possibility. Similarly it is not clear whether the β-lactams formed in the reaction of **8** with Raney nickel[6] arise through a pathway involving diradicals or organonickel intermediates.



Scheme 4

1,4-Diradicals in which the radicals are both centred on sp^3 carbons are known to collapse to cyclobutanes with a high degree of retention of configuration,[7] and given the observation that N–C bond in the enzymatic conversion of the ACV tripeptide into isopenicillin N takes place with retention of configuration,[8] we were interested in investigating the stereochemistry of N–C bond formation in the photochemical generation of β-lactams from tetrahydro-1,2-oxazine-3,6-diones. A sample of tetrahydro-1,2-oxazine-3,6-dione **2** was prepared specifically labelled with deuterium as shown in Scheme 5, using the known stereospecific *cis* deuteriation of maleic anhydride.[9] The ^{1}H nmr spectrum of the labelled tetrahydro-1,2-oxazine-3,6-dione **9**, run with decoupling of the deuterium nuclei, indicated there to be essentially one deuteriated compound present, presumably the *cis* isomer. Photolysis of **9** provided the expected doubly-labelled β-lactam, which appeared to



Scheme 5

be a mixture of both *cis* and *trans* isomers **10** and **11** in approximately equal amounts, as evidenced by the ^{1}H nmr spectrum (run with deuterium decoupling) of the product. It is possible that bond rotation is faster than N–C bond formation in a diradical such as **1**, but other possibilities cannot be ruled out at present.

In conclusion, we have successfully carried out a reaction which was designed to provide the β-lactam ring system *via* an intermediate diradical, and provided evidence that in the case studied, that the product is formed with scrambling of stereochemistry, although the reason for this is not known at present.

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Experimental Section

Melting points were determined using a Reichert hot stage apparatus and are uncorrected. Infra-red spectra were obtained using a Perkin–Elmer 297 spectrophotometer and were calibrated using a polystyrene film. ^{1}H nmr spectra were recorded on Perkin–Elmer R–32 (90 MHz), and Bruker WM 360 (360 MHz) instruments. Deuterium decoupled ^{1}H nmr spectra were measured using a Bruker AM 250 (250 MHz) spectrometer. ^{1}H nmr spectra were measured in $CDCl_3$ or $(CD_3)_2CO$ quoted in ppm (δ_H), and were referenced to residual solvent (250 and 360 MHz) or TMS (90 MHz). The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants (J) were recorded in Hz. Mass spectra were recorded on Varian CH5D and VG 7070 double focusing instruments, and thermospray mass spectra were run on a Finnigan 4500 quadropole spectrometer fitted with a Finnegan thermospray ion source. Hplc was carried out on a Hypersil 5 micron silica column with a mobile phase of 2% ethanol in cyclohexane, using a Waters 6000 pump and uv detector (254 nm). This was also used in hplc-mass spectrometry, connected to a Finnegan 4500 quadropole mass spectrometer *via* a Finnegan moving belt LC-MS interface. Photolyses were performed using a Hanovia quartz immersion well reactor with a 6W low pressure mercury vapour lamp, and an Applied Photophysics all-glass immersion well reactor with a 450W medium pressure mercury vapour lamp. Microanalyses were performed by Mrs. A. Dams, Department of Chemistry, University College, Cardiff. Polygram silica gel G_{254} plates were used for tlc, visualised by uv or phosphomolybdic acid, and flash chromatography was carried out using Merck Keiselgel 60. Petrol refers to light petroleum, fraction boiling 40–60°C. All solvents were dried and distilled before use. All operations involving benzene and carbon tetrachloride were carried out in an efficient fume cupboard.

***N*-Phenyl-*N*-hydroxysuccinamic acid.** Succinic anhydride (10.0g, 0.10mol) was suspended in dichloromethane (30ml) at room temperature and a solution of freshly prepared *N*-phenylhydroxylamine[10] (10.9g, 0.10mol) in dichloromethane (20ml) was added with stirring. After stirring for 16hr the solid product was filtered and dried *in vacuo* to provide the title compound (18.91g, 90.5%) m.p. 107–108°C.

m/z (thermospray) 210 ($M+H^+$, 100%); ν_{max} (nujol) 3200 br, 1720, 1610, 1450, 1260, 1160, 950, 700 cm^{-1}; δ_H ($(CD_3)_2CO$, 90MHz) 2.50–3.00 (4H, m, $(CH_2)_2$), 7.10–7.80 (5H, m, Ar–H); Found: C, 57.20; H, 5.22; N, 6.41. $C_{10}H_{11}NO_4$ requires C, 57.42; H, 5.26; N, 6.70%.

***N*-Phenyltetrahydro-1,2-oxazine-3,6-dione (1).** *N*-Phenyl-*N*-hydroxysuccinamic acid (6.0g, 28.7mmol) was suspended in dichloromethane (30ml) under nitrogen at 0°C and dicyclohexylcarbodiimide (5.9g, 28.7mmol) was added in one portion. After stirring for a further 4h at 0°C the reaction mixture was filtered through Celite, and concentrated *in vacuo* to provide an oily residue. This was extracted with hot carbon tetrachloride (3x20ml) and the extracts concentrated *in vacuo* to provide the title compound as a solid (3.07g, 56%) m.p. 66–68°C; m/z (EI) 191 (M^+ 20%), 175 (10%), 119 (100%), 91 (45%), 84 (95%); ν_{max} ($CHCl_3$) 1790, 1690, 1590, 900 cm^{-1}; δ_H ($CDCl_3$, 90MHz) 2.90 (4H, brs, $(CH_2)_2$), 7.20–7.60 (5H, m, Ar–H); Found: C, 63.08; H, 4.87; N, 7.07. $C_{10}H_9NO_3$ requires C, 62.82; H, 4.75; N, 7.33%.

***N*-Phenylazetidin-2-one (3). Method A** *N*-Phenyltetrahydro-1,2-oxazine-3,6-dione (**3**, 108mg, 0.62mmol) and benzophenone (25mg, 0.14mmol) were dissolved in benzene (130ml) and photolysed (4W Hg lamp, quartz immersion well) under nitrogen. After 5h the reaction mixture was concentrated *in vacuo* and the residue subjected to flash chromatography (petrol:ethyl acetate 3:1) to afford a solid residue which was crystallized (petrol) to give the title compound (21.6mg, 20%) m.p. 76–78°C (lit.[11] m.p. 79°C), identical to a sample prepared by the method of Johnson and Schweitzer.[11] The same yield could also be obtained in the absence of benzophenone as a sensitizer, and also by using a 450W medium pressure mercury lamp and a glass immersion well, which was convenient for larger scale runs (e.g. 0.26g, 1.34 mmol of **3** reacted completely within 1.5h); m/z (EI) 147 (M^+ 80%), 119 (50%), 105 (100%), 104 (65%), 91 (25%); ν_{max} ($CHCl_3$) 1740, 1600, 1500, 1380 cm^{-1}; δ_H ($CDCl_3$, 90MHz) 3.05 (2H, t, J 6.0 Hz, H-3), 3.58 (2H, t, J 6.0 Hz, H-4), 7.20–7.60 (5H, m, Ar–H).

Another run of this reaction was followed by hplc and hplc-mass spectrometry. Calibration curves for detector response were determined for starting material and product. The reaction was sampled at intervals of 5min, ending after 100min, and the concentrations of precursor and product were estimated by hplc and the identity of the peaks confirmed by hplc-mass spectrometry. The concentration of product reached a plateau after about 55–60min, while the precursor concentration continued to fall, implying that the β-lactam was undergoing decomposition under the photolysis conditions.

Method B *N*-Phenyltetrahydro-1,2-oxazine-3,6-dione (**3**, 0.26g, 1.34mmol) was placed in a 5ml round bottomed flask and immersed for 1min in an oil bath preheated to 190°. The reaction mixture was concentrated subjected to flash chromatography (petrol:ethyl acetate 3:1) to afford the title compound (32mg, 16%) as the only product which could be characterised.

***N*-(α-Methylbenzyl)-*N*-hydroxysuccinamic acid.** Succinic anhydride (1.00g, 10mmol) was dissolved in tetrahydrofuran (25ml) at room temperature and after addition of *N*-(α-methylbenzyl)hydroxylamine[12] (1.47g, 10mmol), the mixture was brought to reflux. After 16hr the solvent was removed *in vacuo* to give the title compound (2.32g, 94%) as an amorphous solid which was used in the next step without further purification; m/z (thermospray) 238 ($M+H^+$, 100%); ν_{max} (nujol) 3200 br, 1720, 1610, 700 cm^{-1}; δ_H ($(CD_3)_2CO$, 360MHz) 1.65 (3H, d, J 7.0 Hz, NCHC$\underline{H}_3$Ph), 2.50–3.00 (4H, m, $(CH_2)_2$), 5.05 (1H, q, J 7.0 Hz, NC$\underline{H}$CH_3Ph), 7.10–7.75 (5H, m, Ar–H); Found: C, 60.45; H, 6.19; N, 5.80. $C_{10}H_{11}NO_4$ requires C, 60.75; H, 6.37; N, 5.91%.

***N*-(α-Methylbenzyl)tetrahydro-1,2-oxazine-3,6-dione (2).** *N*-(α-Methylbenzyl)-*N*-hydroxysuccinamic acid (**1**, 2.23g, 92mmol) was suspended in ethyl acetate (50ml) under nitrogen at 0°C and dicyclohexylcarbodiimide (1.9g, 92mmol) was added in one portion. After stirring for 1h at 0°C the reaction mixture was filtered through Celite, and concentrated *in vacuo* to provide an oily residue. This was extracted with hot carbon tetrachloride (3x20ml) and the extracts concentrated *in vacuo* to provide the title compound as an oil (0.88g, 43%); ν_{max} (CCl_4) 1790, 1690, 900 cm^{-1}; δ_H ($CDCl_3$, 90MHz) 1.68 (3H, d, J 7.0 Hz, NCHC$\underline{H}_3$Ph), 2.68 (s, 4H, $(CH_2)_2$), 5.80 (1H, q, J 7.0 Hz, NC$\underline{H}$CH_3Ph), 7.30–7.46 (5H, m, Ar–H).

***N*-(α-Methylbenzyl)azetidin-2-one (4).** *N*-(α-Methylbenzyl)tetrahydro-1,2-oxazine-3,6-dione (**2**, 69mg, 0.30mmol) was dissolved in benzene (140ml) and photolysed (4W Hg lamp, quartz immersion well) under nitrogen. After 5 days the reaction mixture was concentrated *in vacuo* and the residue subjected to flash chromatography (petrol:ethyl acetate 2:1) to give the title compound (11.6mg, 21%); ν_{max} (CCl_4) 1740, 1700 cm^{-1}; δ_H ($CDCl_3$, 360MHz) 1.54 (3H, d, J 7.0 Hz, NCHC$\underline{H}_3$Ph), 2.55–3.30 (4H, m, $(CH_2)_2$), 4.94 (1H, q, J 7.0 Hz, NC$\underline{H}$CH_3Ph), 7.20–7.60 (5H, m, Ar–H).

***N*-Phenyl-*cis*-2,3-dideuterio-*N*-hydroxysuccinamic acid.** This was prepared as above from *cis*-dideuteriosuccinic anhydride[9] (2.0g, 19.6mmol) and phenylhydroxylamine[10] (2.13g, 19.6mmol) to provide the title compound (3.68g, 89%) (> 95% D_2 as estimated by mass spectrometry); δ_H ($(CD_3)_2CO$, 90MHz) 2.50–3.00 (4H, m, $(CDH)_2$), 7.10–7.80 (5H, m, Ar–H).

***N*-Phenyl-*cis*-4,5-dideuteriotetrahydro-1,2-oxazine-3,6-dione (9).** This was prepared as above from *N*-phenyl-*cis*-2,3-dideuterio-*N*-hydroxysuccinamic acid (1.05g, 4.98mmol) and dicyclohexylcarbodiimide (1.03g, 4.98mmol) to provide the title compound (0.44g, 46%) m.p. 67–68°C (> 95% D_2 as estimated by mass spectrometry, and a single stereoisomer as estimated from the deuterium decoupled 250MHz ^1H nmr spectrum); δ_H ($CDCl_3$, 360MHz) 2.82 (1H, brs, H-3), 2.92 (1H, brs, H-4), 7.28 (1H, t, J 7.0 Hz, *p*-Ar–H), 7.35 (2H, apparent t, J 7.0 Hz, *m*-Ar–H), 7.48 (2H, d, J 7.0 Hz, *o*-Ar–H). Deuterium decoupling of the ^1H nmr spectrum run at 250MHz showed the peaks at 2.82 and 2.92 as clean doublets, J 4.9 Hz.

***cis* and *trans*-*N*-Phenyl-3,4-dideuterioazetidin-2-one (10 and 11).** Photolysis of *N*-Phenyl-*cis*-4,5-dideuteriotetrahydro-1,2-oxazine-3,6-dione (**9**, 250mg, 1.30mmol) in benzene (250ml) (450W Hg lamp, glass immersion well) for 30min and purification as above gave the title compound (47.5mg, 19%) m.p. 76–78°C (> 90% D_2 as estimated by mass spectrometry); δ_H ($CDCl_3$, 360MHz) 3.10 (1H, br s, H-3), 3.61 (1H, apparent brd, J~5.0 Hz, H-4), 7.06–7.53 (5H, m, Ar–H). Deuterium decoupling of the ^1H nmr spectrum run at 250MHz showed the signal at 3.10 as two doublets, with J 3.2 Hz and 6.0 Hz, corresponding to the *trans*- and *cis*- isomers respectively, in a ratio of approximately 1:1.

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