The First Example of a Transoid Amide (Imide) in an Eight-membered Lactam

P. Andrew Evans,†[a] Andrew B. Holmes,*[a] Ian Collins,†[a] Paul R. Raithby[a] and Keith Russell†[b]

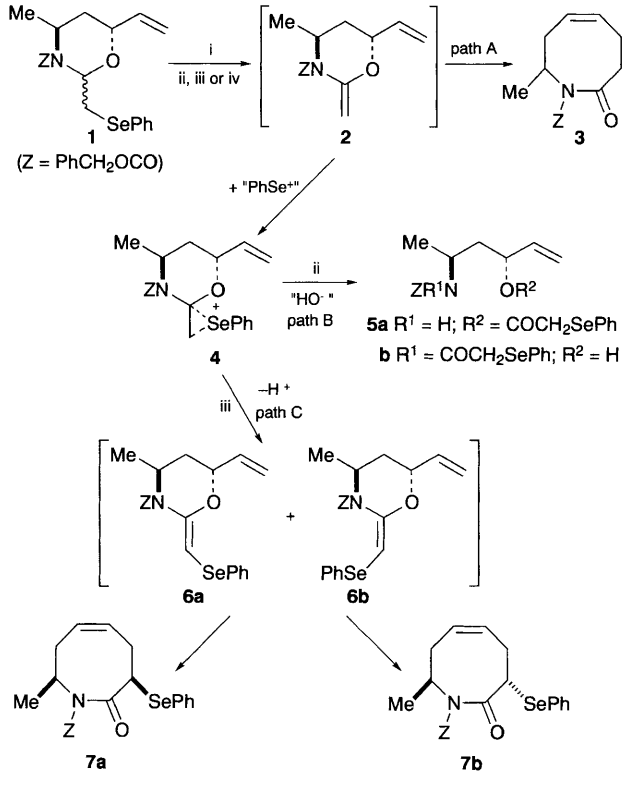
[a] *Cambridge Centre for Molecular Recognition, University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW*

[b] *Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK SK10 4TG*

The Claisen rearrangement of the ketene aminal derived by selenoxide elimination of the seleno-aminal **1** in refluxing toluene in the presence of dihydropyran yields the expected unsaturated eight-membered lactam derivative **3**, as well as two unexpected products **7a** and **7b**; the major product **7a** (resulting from a selenium re-addition reaction) was shown by X-ray crystallography to be a highly distorted transoid amide (imide) with the largest p-orbital distortion (τ = 50.6°) recorded for a cyclic amide.

The correlation of amide activation with reactivity can provide substantial insight into the design of transition state analogues for amide cleavage in biological systems. Highly strained lactams are of considerable interest as models for the study of amide *cis–trans* isomerisation. Lactams therefore provide excellent model systems for the study of the amide group in a constrained environment. The distortion can result from either pyramidalisation at nitrogen or p-orbital torsion.[1,2] Large ring lactams prefer the planar *trans*-conformation, the crosssover point to *cis* being for the nine-membered lactam‡ as observed by Huisgen[3] using an analysis of the IR stretching frequency of the lactam carbonyl group.[4] Numerous other studies have also been conducted, with a notable contribution by Williamson and Roberts,[6] on the use of ^{13}C NMR spectra in the conformational analysis of these systems.

Until the present work crystal structures of lactams of ring size ≤8 have always indicated an exclusive preference for the *cis* planar conformation.[4] We report the use of a novel Claisen rearrangement to prepare the highly strained *N*-benzyloxycarbonyl substituted lactam **7a** which has the largest p-orbital distortion ever reported in a lactam, resulting in a 'transoid' nonplanar amide (imide) in an eight-membered ring (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) $NaIO_4$, $NaHCO_3$, MeOH–H_2O, *ca.* 20 °C, 1 h (>95%); (ii) 1,8-diazabicyclo[5.4.0]undecene (DBU) (3 equiv.), toluene, heat 16 h to give **3** (58%) and **5a**, **b** (22%); (iii) Dihydropyran (DHP), toluene, heat 16 h to give **3** (17%), **7a** (46%) and **7b** (5%); (iv) TBDMSOC(OMe)=CH_2 (20 equiv.), DBU (3 equiv.), toluene, heat 16 h to give **3** (80%) and $PhSeCH_2COOMe$ (76%)

Our approach to monocyclic medium ring lactams[7] was *via* a Claisen rearrangement[8] of the ketene aminal **2** which was generated by *in situ* elimination of the selenoxide derived from **1**. A major side reaction in selenoxide eliminations is the readdition of a selenium electrophile, generated by disproportionation of PhSeOH. This is usually minimised by carrying out the elimination in the presence of the base 1,8-diazabicyclo[5.4.0]undecene (DBU).[7] When the selenoxide derived from the racemic *anti*-diastereoisomer **1** was heated in refluxing toluene in the presence of DBU (Scheme 1, reagent ii), a modest yield of the expected racemic *N*-benzyloxycarbonyl lactam **3** was obtained. The main byproducts were the imide **5a** and the ester **5b** which were derived from the formal addition of PhSeOH to the ketene aminal **2**, followed by ring opening of the resulting *ortho*-ester. Evidently the high nucleophilicity of **2** promoted the selenium re-addition. Reasoning that the selenium elimination products could be intercepted with an excess of an electron rich alkene we carried out the elimination–Claisen rearrangement in the presence of dihydropyran (DHP) (25 equiv.) (Scheme 1, reagent iii).§ This afforded a small amount of the lactam **3** (17% yield) and the novel seleno-substituted *N*-benzyloxycarbonyl lactams **7a** and **7b** in 46% and 5% yields respectively. The formation of the last two products may be rationalised as follows. Ketene aminal **2** can either undergo [3.3] sigmatropic rearrangement (path A) to afford the lactam **3**, or readdition of a selenium electrophile *via* the episelenonium ion **4**. In the presence of DBU (reagent ii) capture by hydroxide and *ortho*-ester collapse afforded **5a**, **b** (path B). In dihydropyran in the absence of DBU (path C, reagent iii) proton loss led to the vinyl selenides **6a** and **6b**. The (*Z*)-intermediate **6a** is presumably preferred because unfavourable $A^{1,3}$-interactions with the *N*-benzyloxycarbonyl group are avoided. The selenides **6a** and **6b** both undergo stereospecific Claisen rearrangement to form a 9:1 mixture of the seleno-substituted lactams **7a** and **7b**.

The major lactam **7a** formed crystals suitable for X-ray crystallographic analysis.¶ The molecular structure of **7a** (Fig. 1) confirmed the *cis*-relative stereochemistry of the side chains

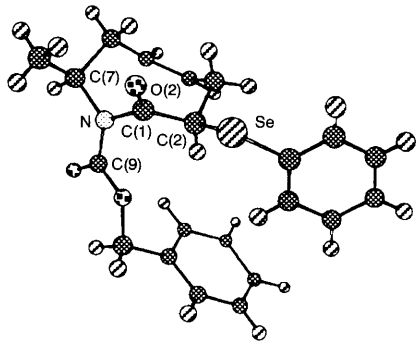


Fig. 1 The molecular structure of the lactam **7a** as determined by X-ray crystallography

and the distorted geometry of the (*Z*)-alkene. The most intriguing feature was the highly strained 'transoid' ring *N*-benzyloxycarbonyl amide. This is clearly illustrated by a projection of the amide along the C(O)–N bond (Fig. 2).

A good measure of p-distortion is the twist angle τ‖ of the C(O)–N bond,[1,2,9] which is 50.6°. By comparison some representative twist angles for cyclic amides **8**[10] and **9**[5,9] and analogous acyclic derivatives **10**[11] and **11**[12] are illustrated in Fig. 3. Thus the eight-membered lactam **7a** has the most twisted (*N*-acyl) amide linkage reported for a monocyclic system, although the exocyclic *N*-acyl substituted thiazolidinone **10** is a slightly more distorted acyclic amide.[11]

The distortion in **7a** is the result of both steric and electronic factors. Cyclo-di-β-alanyl **12** is chair-shaped, but the lactam linkages are *cis*-planar.[13] The lactam **7a** is formally related to **12** by replacement of one amide linkage in the latter with a (*Z*)-alkene. It also assumes a chair conformation; the substituents at positions 3 and 8 (2 and 7 in the numbering used in Fig. 1) are pseudo-equatorial, but the amide is distorted. This severe distortion, in which the ring carbonyl is directed back over the ring, presumably arises to avoid the allylic strain which would result from having both the ring amide and the urethane C(O)–N linkages coplanar. The nitrogen lone pair electrons are evidently satisfied by conjugation solely with the exocyclic benzyloxycarbonyl group. The activation of amide carbonyl groups to nucleophilic attack by conversion into *N*-*tert*-butyloxycarbonyl imides has been exploited as a method for amide cleavage.[14,15] Carbamate-protected lactams related to **7** show enhanced susceptibility to nucleophilic attack. This is in accord with the hypothesis that p-distortion effects as well as pyramidalisation of amide nitrogen atoms (as observed in bridgehead lactams) can be significant in enhancing nucleophilic cleavage of amide bonds.[16]

Finally, we note that selenium readdition to the intermediate ketene aminal **2** can essentially be completely suppressed by carrying out the Claisen rearrangement in the presence of excess of the *tert*-butyldimethylsilyl ketene acetal derived from the *O*-silylation of the enolate of methyl acetate, to afford the eight-membered lactam **3** in excellent yield with the selenium elimination product being trapped as methyl phenylselenoacetate (Scheme 1, reagent iv). We believe that the ketene acetal will have general synthetic utility as a nucleophilic trapping reagent in selenoxide eliminations where unwanted side reactions of the selenium elimination product are problematic.[8]

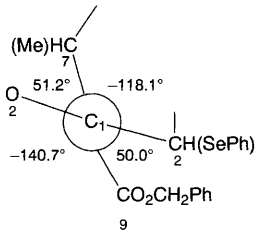


Fig. 2 Projection along the C(O)–N lactam bond in **7a**

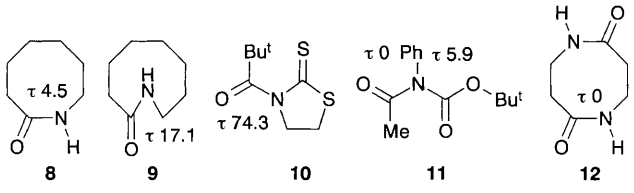


Fig. 3 Some twist angles τ of representative amides **8–12**

We thank the EPSRC, Zeneca Pharmaceuticals (Alderley Park) and Merck, Sharp and Dohme (Terlings Park) (CASE awards to P. A. E. and I. C.) for supporting this work. We thank EPSRC (Dr J. Ballantine) for provision of the Swansea Mass Spectrometry Service, The Royal Society for the award of a Royal Society Leverhulme Senior Research Fellowship (A. B. H.) and Pfizer Central Research (Sandwich) for generous financial support. We thank Dr R. Baker (Merck) and Dr P. Whittamore (Zeneca) for their interest in this work, Professors J. D. Dunitz and K. J. Shea and Dr T. G. Lease for helpful discussions, and Mr Stuart Walker for assistance with the X-ray analysis.

Received, 4th September 1995; Com. 5/04663G

Footnotes

† Present address: Department of Chemistry and Biochemistry, University of Delaware, Newark DE 19716, USA (P. A. E.), Merck Sharp & Dohme, Terlings Park, Harlow, UK CM20 2QR (I. C.), Zeneca Pharmaceuticals, 1800 Concord Pike, Wilmington DE 19897, USA (K. R.).

‡ The nine-membered lactam (caprylolactam) was reported as *trans* in the crystalline state, but exists as a (4 : 1) *cis* : *trans* equilibrium mixture in dilute chloroform solution, with the *cis*-conformer predominating.[3] Caprylolactam hydrochloride has a near planar *cis*-configuration.[5]

§ We thank Dr W. Watkins for this suggestion.

¶ Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‖ The twist angle τ is calculated according to the method of Winkler and Dunitz:[9] $\tau = 1/2(\omega_1 + \omega_3)$ where ω_1 and ω_3 are the respective torsion angles C_2–C_1–N–C_9 and O_2–C_1–N–C_7 (Fig. 2).

References

1 For an introduction and an account of the effect of amide distortion in bridgehead lactams see T. G. Lease and K. J. Shea, *J. Am. Chem. Soc.*, 1993, **115**, 2248.
2 T. G. Lease and K. J. Shea, in *Advances in Theoretically Interesting Molecules*, ed. R. P. Thummel, JAI, Greenwich, CT, vol. 2, 1992, pp. 79–112.
3 R. Huisgen, H. Brade, H. Walz and I. Glogger, *Chem. Ber.*, 1957, **90**, 1437.
4 H. E. Hallam and C. M. Jones, *J. Mol. Structure*, 1970, **5**, 1.
5 F. K. Winkler and J. D. Dunitz, *Acta Crystallogr.*, 1975, **B31**, 276, 278.
6 K. L. Williamson and J. D. Roberts, *J. Am. Chem. Soc.*, 1976, **98**, 5082.
7 P. A. Evans, A. B. Holmes and K. Russell, *Tetrahedron Lett.*, 1992, **33**, 6857; P. A. Evans, A. B. Holmes and K. Russell, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3397.
8 M. Petrzilka, *Helv. Chim. Acta*, 1978, **61**, 3075; M. S. Congreve, A. B. Holmes, A. B. Hughes and M. G. Looney, *J. Am. Chem. Soc.*, 1993, **115**, 5815.
9 F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169.
10 F. K. Winkler and P. Seiler, *Acta Crystallogr.*, 1979, **B35**, 1920.
11 S. Yamada, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1083.
12 J. Symersky, P. Malon, L. Grehn and U. Ragnarsson, *Acta Crystallogr.*, 1990, **C46**, 683.
13 D. N. J. White and J. D. Dunitz, *Israel J. Chem.*, 1972, **10**, 249.
14 L. Grehn, K. Gunnarsson and U. Ragnarsson, *J. Chem. Soc., Chem. Commun.*, 1985, 1317.
15 J. Ezquerra, J. de Mendoza, C. Pedregal and C. Ramirez, *Tetrahedron Lett.*, 1992, **33**, 5589.
16 Q.-P. Wang, A. J. Bennet, R. S. Brown and B. D. Santarsiero, *J. Am. Chem. Soc.*, 1991, **113**, 5757.