

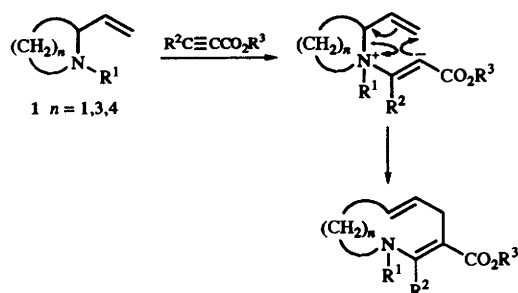
Ring expansion reactions of isoquinoline derivatives to 2-benzazocine and 3-benzazecine derivatives

Mostafa M. M. Bamatraf, John M. Vernon* and Giles D. Wilson

Department of Chemistry, University of York, Heslington, York, UK YO1 5DD

Reaction of 2-methyl-1-vinyl-1,2-dihydro- and 1,2,3,4-tetrahydroisoquinolines with dimethyl acetylenedicarboxylate gives 1:1 adducts, which are 2-benzazocine and 3-benzazecine diesters, respectively.

The reaction of acetylenic esters with tertiary allylic amines involves [3,3] sigmatropic rearrangement of an intermediate zwitterion.^{1,2} The same reaction with 2-vinyl heterocyclic tertiary amines 1 results in the ring expansion by four atoms outlined in Scheme 1. This was first reported for 3-membered

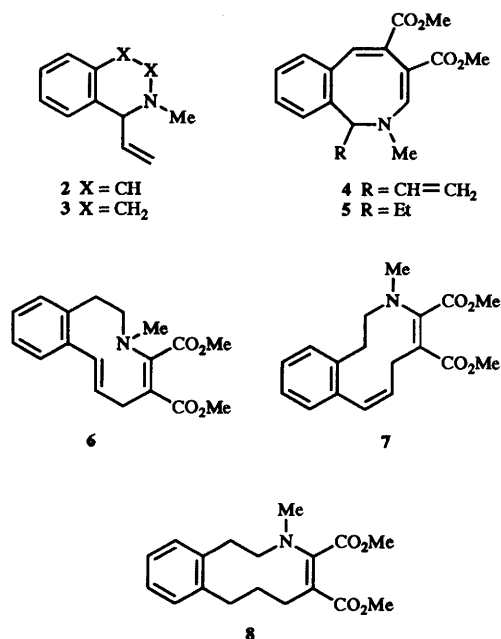


Scheme 1

and more recently for 5- and 6-membered cyclic amines.^{3,4} Closely related reactions which are less clearly ring expansions are known for some bicyclic and polycyclic amines.^{5,6} We report two contrasting ring expansion reactions of isoquinoline derivatives with dimethyl acetylenedicarboxylate (DMAD).

2-Methyl-1-vinyl-1,2-dihydroisoquinoline 2 was obtained by addition of vinyl Grignard reagent to 2-methylisoquinolinium iodide. The amine 2 reacted exothermically with DMAD in dry acetonitrile to give 61% yield of a pale yellow crystalline 1:1 adduct. The ¹³C NMR DEPT spectrum showed only a single CH₂ resonance at δ 121.0, suggesting the vinyl group of 2 was still present. This was confirmed by hydrogenation to give a dihydro derivative, for which ¹H and ¹³C NMR signals showed the presence of ethyl as well as *N*-methyl and two *O*-methyl groups. Although the ¹H NMR spectrum of the 1:1 adduct is complex and not easily interpreted, other evidence is consistent with the 2-benzazocine structure 4 and with 5 for the dihydro derivative. Structure 4 was confirmed by X-ray crystallography (Fig. 1). Although the formation of 4 from 2 and DMAD was an unexpected result, there are clear precedents for this pattern of ring expansion in the reaction of enamines,⁷ including indoles,⁸ 1,2-dihydropyridines⁹ and 1,4-dihydroquinolines,¹⁰ with DMAD or propiolate esters.

Successive addition of methyl iodide, then vinyl Grignard reagent, to 3,4-dihydroisoquinoline afforded the tetrahydroisoquinoline 3. From the reaction of 3 with DMAD in freshly distilled chloroform in the presence of a catalytic amount of camphorsulfonic acid (*cf.* conditions employed by Vedejs *et al.*⁴) two products were separated chromatographically in 6 and 29% yield. Both were yellow oils, 1:1 adducts C₁₈H₂₁NO₄, with ¹H and ¹³C NMR spectra consistent with the 3-benzazecine structures 6 and 7. In particular, the structures were assigned by reference to the resonance for 8-H at δ 6.48 (d, *J* 10.9 Hz) for the minor product, *cis*-isomer 7, and at δ 6.38 (d, *J* 16.5 Hz) for the



major product, *trans*-isomer 6. On hydrogenation, both 6 and 7 gave the same dihydro derivative 8, which was characterised by the molecular ion (M⁺ 317) in its mass spectrum and by the presence of signals for five CH₂ groups in the ¹³C NMR DEPT spectrum.

Formation of the benzazecine derivatives 6 and 7 provides a new example of ring expansion by four atoms to access a 10-membered ring, as in Scheme 1. Further ring expansion reactions of the amine 3 are under investigation and will be reported in due course.

Experimental

2-Methyl-1-vinyl-1,2-dihydroisoquinoline 2

Vinylmagnesium chloride (67 mmol) in tetrahydrofuran (THF) (40 cm³) was added dropwise to 2-methylisoquinolinium iodide (9.2 g, 34 mmol) in THF, stirred under nitrogen. The mixture was heated to reflux temperature and then cooled, after which saturated aqueous ammonium chloride was added to it. The mixture was then extracted with ether and the extract dried and evaporated under reduced pressure. The residue was distilled to give the 1,2-dihydroisoquinoline 2 (3.8 g, 65%) as an oil, bp 92 °C at 0.4 mmHg, which was analysed by GC (single component on SE 54 stationary phase) and GC-MS, *m/z* 171 (M⁺, 14%) and 144 (M - C₃H₂, 100%).

Dimethyl 2-methyl-1-vinyl-1,2-dihydro-2-benzazocine-4,5-dicarboxylate 4

DMAD (3.0 g, 21 mmol) was added dropwise to the amine 2 (0.7

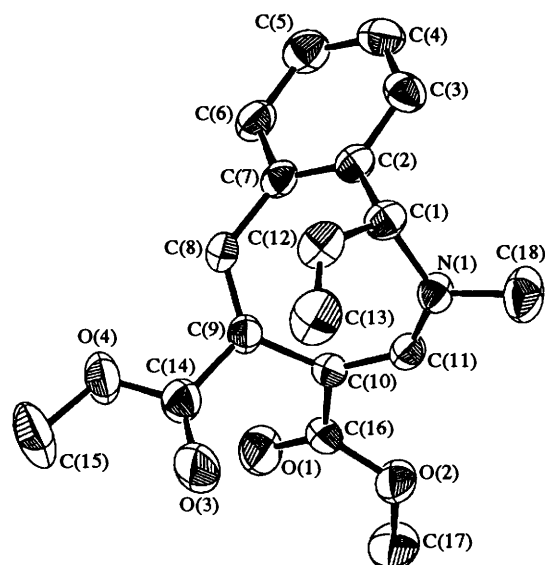


Fig. 1 ORTEP drawing of the structure of compound 4 with crystallographic numbering scheme (hydrogen atoms omitted)

g, 4 mmol) in dry acetonitrile (2 cm³). GC analysis after several minutes showed complete disappearance of 2. The mixture was chromatographed on neutral alumina, from which ether–light petroleum (1:1, v/v) eluted the 1,2-dihydro-2-benzazocine 4, which was obtained as pale yellow crystals (0.76 g, 61%), mp 161–161.5 °C (from methanol) (Found: M⁺, 313.131 12. C₁₈H₁₉NO₄ requires M, 313.131 41).

Dimethyl 1-ethyl-2-methyl-1,2-dihydro-2-benzazocine-4,5-dicarboxylate 5

The adduct 4 (170 mg) in methanol (25 cm³) with palladium-on-charcoal (10% Pd; 50 mg) was stirred under hydrogen until analysis by GC on SE54 stationary phase showed disappearance of 4. The solution was filtered and the filtrate evaporated to give the dihydro derivative 5 as a pale yellow oil (130 mg, 76%); δ_H(CDCl₃) 0.87 (3 H, t, J 7.3 Hz, CH₃CH₂), 1.98 (2 H, m, CH₂CH₃), 2.88 (3 H, s, NCH₃), 3.59 and 3.81 (each 3 H, s, OCH₃), 5.70 (1 H, t, J 7.7 Hz, 1-H), 7.24–7.34 (5 H, m, ArH and 6-H) and 7.45 (1 H, s, 3-H); δ_C 11.0 (CH₃), 22.2 (CH₂), 36.6, 50.9 and 51.9 (CH₃), 58.1 (CH), 95.0 (C), 124.4, 127.7, 129.4, 134.0, 134.8, 136.3, 138.0, 152.2 and 168.9 and 169.5 (C=O); m/z 315 (M⁺, 100%), 300 (M – CH₃, 90), 256 (62) and 182 (52).

Crystal data and structure determination for compound 4

C₁₈H₁₉NO₄, M = 313.3, orthorhombic, space group

P2₁2₁2₁, a = 12.776(10), b = 17.200(5), c = 7.4384(12) Å, V = 1634.6(14) Å³, Z = 4, D_c = 1.273 g cm⁻³, F(000) = 664, μ(Mo-Kα) = 0.90 cm⁻¹, crystal size 0.3 × 0.25 × 0.2 mm.

Intensity data were collected at 293 K on a Rigaku four-circle diffractometer with graphite-monochromated Mo-Kα X-radiation, λ = 0.7107 Å. Equivalent reflections were merged and only Lorentz and polarisation corrections were applied. The structure was solved by direct methods using SHELXS¹¹ and refined on F² using SHELXL.¹² Full-matrix least-squares refinement of 212 parameters for 2186 independent reflections [I ≥ 2σ(I)] in the range 2.86 < θ < 25° gave R₁ = 0.0355 and wR₂ = 0.0892. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre [see Instructions for Authors (1995), *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue No. 1].

Acknowledgements

M. M. M. B. acknowledges a scholarship from the University of Aden.

References

- 1 K. A. Kandeel and J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2023.
- 2 A. L. Schwan and J. Warkentin, *Can. J. Chem.*, 1988, **66**, 1668.
- 3 A. Hassner and R. D'Costa, *Tetrahedron Lett.*, 1981, **22**, 3694.
- 4 E. Vedejs and M. Gingas, *J. Am. Chem. Soc.*, 1994, **116**, 579.
- 5 F.-A. Kunng, J.-M. Gu, S. Chao, Y. Chen and P. S. Mariano, *J. Org. Chem.*, 1983, **48**, 4262.
- 6 K. Hayakawa, S. Motohiro, I. Fujii and K. Kanematsu, *J. Am. Chem. Soc.*, 1981, **103**, 4605; K. Hayakawa, I. Fujii and K. Kanematsu, *J. Org. Chem.*, 1983, **48**, 166; A. Singh, S. Archer, K. Hoogsteen and J. Hirschfield, *J. Org. Chem.*, 1983, **48**, 173.
- 7 G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, 1963, **28**, 1459; K. C. Brannock, R. D. Burpitt, V. W. Goodlett and J. G. Thweatt, *J. Org. Chem.*, 1963, **28**, 1464; C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson and P. Strachan, *J. Org. Chem.*, 1963, **28**, 3134.
- 8 R. M. Acheson, J. N. Bridson and T. S. Cameron, *J. Chem. Soc., Perkin Trans. 1*, 1972, 968.
- 9 R. M. Acheson, G. Paglietti and P. A. Tasker, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2496.
- 10 P. G. Lehman, *Tetrahedron Lett.*, 1972, 4863.
- 11 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
- 12 G. M. Sheldrick, SHELXL-93 program for crystal structure refinement, University of Göttingen, Germany, 1993.

Paper 5/022781

Received 10th April 1995

Accepted 1st May 1995