

A One-pot Three Carbon Decarboxylative Ring Expansion of Cyclic Secondary Amino Acids. X-Ray Crystal Structure of a Substituted 1-Azacyclo-octa-2,4-diene

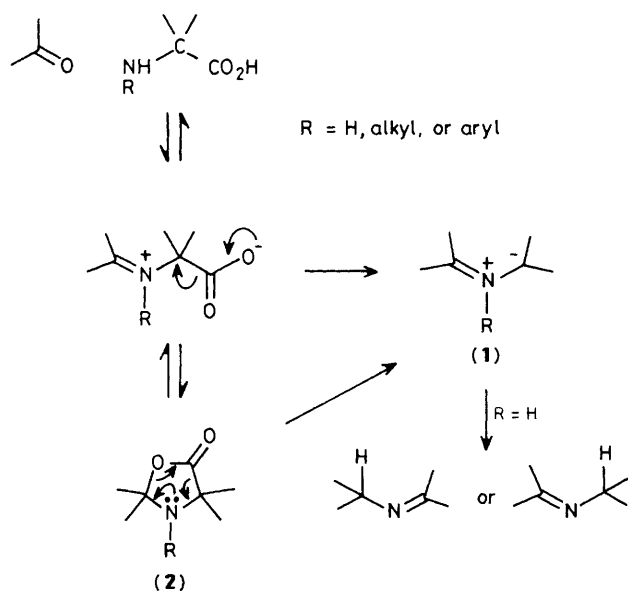
Harriet Ardill, Ronald Grigg,* Visuvanathar Sridharan, and John Malone

Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland

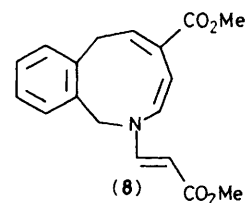
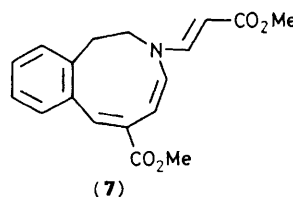
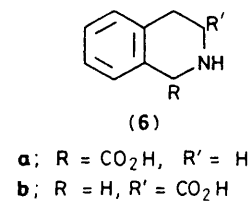
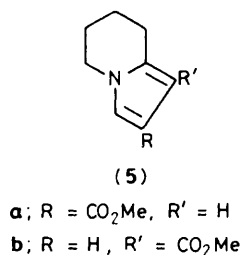
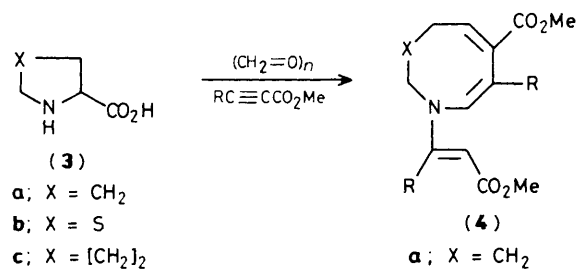
Heating cyclic secondary α -amino acids with an excess of paraformaldehyde or formalin and methyl propiolate or dimethyl acetylenedicarboxylate leads to a decarboxylative ring expansion giving 8- and 9-membered cyclic aza-dienes *via* an azomethine ylide; the X-ray crystal structure of a substituted 1-azacyclo-octa-2,4-diene shows it to have an irregular tub conformation.

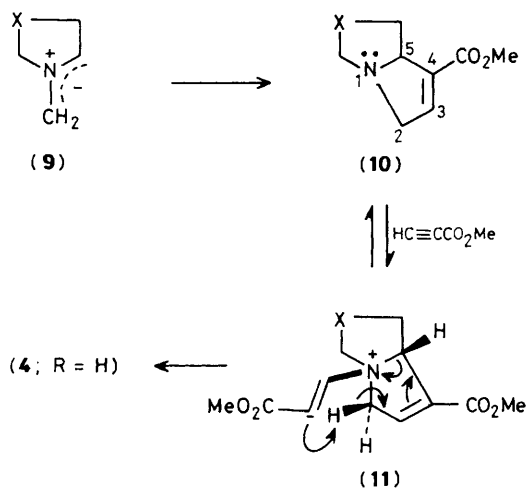
We have recently shown that the Strecker degradation and decarboxylative transamination (Scheme 1) involve an intermediate azomethine ylide (1), which subsequently undergoes a kinetically controlled proton transfer from nitrogen to carbon, depending on the electron density at the two carbon sites (Scheme 1), to give imine products. Evidence for the intermediacy of the azomethine ylide was provided by trapping in a wide range of 1,3-dipolar cycloaddition reactions.¹ The reaction tolerates wide variations in carbonyl

(formaldehyde, aliphatic and aromatic aldehydes, and aliphatic and aromatic ketones) and dipolarophile components, and occurs with all types of α -amino acid (primary, secondary,



Scheme 1





α,α -disubstituted, cyclic, and acyclic) except tertiary amino acids. More recently, extended studies of the stereochemistry and mechanism of these processes indicates they proceed *via* an oxazolidin-5-one (2) (Scheme 1) which undergoes a stereospecific 1,3-dipolar cycloreversion.^{2,3} The relevance of this process to pyridoxal-mediated enzymic decarboxylation has been emphasised.^{1,4}

In certain cases the initially formed cycloadducts react further to give interesting ring-expanded products. Thus when proline (3a) (1 mol) is heated in toluene (100 °C; 4 h) with an excess of paraformaldehyde (5 mol) and methyl propiolate (4 mol), the ring-expanded product (4a; R = H) is obtained in excellent yield (quantitative by n.m.r.; 78% isolated). The same reaction occurs when formalin is used in place of paraformaldehyde. When dimethyl acetylenedicarboxylate is used in place of methyl propiolate (toluene; 100 °C; 15 h) the product (31%) is (4a; R = CO₂Me). The thiazolidine (3b) similarly gives (4b; R = H) in 24% yield. Piperidine-2-carboxylic acid (3c) requires the addition of 10% dibutyltin(IV) dichloride as a mild Lewis acid to promote reaction (toluene; 100 °C; 16 h) with paraformaldehyde and methyl propiolate; under these conditions (4c; R = H) is obtained in 23% yield. In addition to (4c) the two pyrroles (5a and b) are obtained in 17 and 4% yield, respectively. Both tetrahydroisoquinoline-1- and 3-carboxylic acids (6a and b) react in a similar manner (toluene; 100 °C; 10% Bu₂SnCl₂; 16 h) to give (7) (<10%) and (8) (21%), respectively.

The mechanism of this remarkable ring expansion involves formation of an azomethine ylide [e.g. (9)] as outlined in Scheme 1. 1,3-Dipolar cycloaddition of (9) with methyl propiolate can give rise to two regioisomers. The dipole-dipolarophile frontier orbital interactions are expected to be similar for both regioisomeric transition states and a preference for (10) arises from steric factors, with 2,3-bond formation being more advanced than 4,5-bond formation in the transition state leading to cycloadducts. Substantial amounts of the other regioisomer are formed in some cases, as shown by the isolation of (5a). Michael addition of the lone pair of the bridgehead nitrogen atom in (10) to methyl propiolate then generates the zwitterion (11) which can fragment (11; arrows) to product (4; R = H). A related Δ^3 -pyrroline to pyrrole rearrangement has been previously reported by us,⁵ and Mariano *et al.*⁶ and Kanematsu⁷ have utilised a zwitterion analogous to (11) in zwitterionic amino-Claisen rearrangements (Scheme 2) in alkaloid chemistry.

The medium-sized ring products (4), (7), and (8) show fluxional behaviour in their ¹H n.m.r. spectra, and this is being

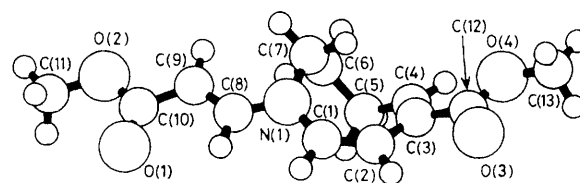
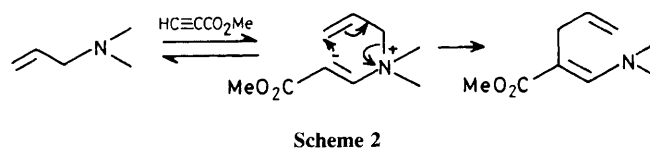


Figure 1. X-Ray crystal structure of (4a; R = H).

studied further, e.g. the spectrum (250 MHz) of (4a; R = H) (CDCl₃) exhibits broad signals at δ 1.57 (CH₂CH=C) and 3.56 (CH₂N). To provide a sound structural basis for the n.m.r. studies the X-ray crystal structure of (4a; R = H) was determined (Figure 1).†

The ring is in the shape of an irregular tub, with a torsion angle of -40.8° between the two ring double bonds. The *trans*-configuration of the side-chain double bond is confirmed. All the torsion angles obtained from our X-ray data correspond closely with those derived by Allinger *et al.*⁹ from force-field calculations on cyclo-octa-1,3-diene but differ noticeably from the torsion angles derived from an electron diffraction study reported by Traetteberg.¹⁰ Allinger's calculations showed that the irregular tub conformation for cyclo-octa-1,3-diene is nearly equal in energy to an alternative C₂ conformation, and n.m.r. studies are in hand on the fluxional medium-sized ring heterocycles reported here.

† Crystal data for (4a; R = H); C₁₃H₁₇NO₄, *M* = 251.3, monoclinic, space group *P*2₁/*c*, *a* = 14.135(14), *b* = 11.194(11), *c* = 8.915(9) Å, β = 103.8(1)°, *U* = 1369.9 Å³, *D_c* = 1.22 g cm⁻³, *Z* = 4, *F*(000) = 536, μ (Mo-K α) = 0.55 cm⁻¹.

Crystals were very thin, colourless plates and were shown by preliminary photographic characterization (oscillation and Weissenberg; Cu-K α radiation) to consist of parallel rotation twins (twin axis *c*). Reciprocal lattice points for the twin pair coincided only for reflections with *l* = 4*n* and therefore it was possible to collect intensity data from one twin for data with *l* \neq 4*n*. A crystal of dimension 1.0 \times 0.9 \times 0.05 mm was mounted with the twin axis (*c*) coincident with the ω axis of a Stöe STAD12 two-circle diffractometer. By using graphite-monochromated Mo-K α radiation and the background- ω scan-background technique, intensity data from one twin were recorded for layers *hk*0-3 and *hk*5-6; *hk*4 data were neglected as coincident reflections were not symmetry-equivalent. Coincident reflections for *hk*0 were symmetry-equivalent and thus, in order to put all data on a common scale, only half the measured intensity was deemed to arise from the single twin. 1017 unique data (*l* > 0) were corrected for Lorentz and polarization effects and the structure was solved by direct methods using SHELX.⁸ The 524 reflections with *I* > 3 σ (*I*) were employed in the subsequent least-squares refinement. Anisotropic vibrations were allowed for non-hydrogen atoms; hydrogen atoms were included at positions calculated from the geometry of the molecule (C-H 1.08 Å) and common isotropic temperature factors for methyl, methylene, and olefinic hydrogen atoms refined to final values of 0.17(3), 0.11(2) and 0.09(a) Å², respectively. The final conventional *R* was 0.095. Atomic co-ordinates, thermal parameters, and bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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