

On the Mechanism of Thermal Ring Expansion of 3,3-Dialkylloxindoles

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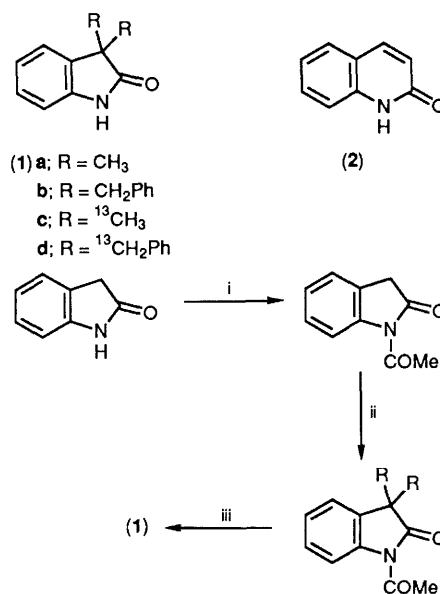
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^{13}C Labelling experiments show that the title reaction takes place by a free radical mechanism which involves (i) homolysis of the C(3)–alkyl bond, (ii) rearrangement of the resulting 3-indolyl radical to a 3-indolylmethyl radical [e.g., (7)], (iii) ring expansion by competitive neophyl rearrangement or attack at the carbonyl position, and (iv) aromatisation by loss of a hydrogen atom.

As part of a general study of the pyrolysis of oxindole derivatives, Brown and Butcher discovered in 1973 that 3,3-dimethylloxindole (**1a**) undergoes an unexpected ring-expansion reaction to give quinolin-2-one (**2**) under flash-vacuum-pyrolysis (FVP) conditions.¹ Although behaviour of this type was, and still is, unique and unprecedented, the mechanistic and synthetic implications of the transformation have remained unexplored. Here the results of ^{13}C labelling experiments are presented, which resolve the first of these questions with particular reference to (**1a**) and its 3,3-dibenzyl analogue (**1b**).

The substrates (**1**) were made by simple modification of literature methods² (Scheme 1). Flash vacuum pyrolysis of the 3,3-dimethyl derivative in our apparatus required 900 °C to give the quinolin-2-one (**2**) as reported,¹ whereas the 3,3-dibenzyl compound, at only 650 °C, gave a 3.0:1.0 mixture of 3- and 4-phenylquinolinones (**3**) and (**4**) (Scheme 2). The formation of bibenzyl,³ and the lower pyrolysis temperature in the latter case clearly indicate homolytic cleavage of one 3-substituent. The subsequent formation of two quinolinones from the resulting 3-indolyl radical (**5**) shows that there are at least two competing pathways to the products.

This dichotomy can be rationalised by two possible mechanisms (Schemes 3 and 4) which differ in the timing of the ring



Scheme 1. Reagents: i, Ac₂O; ii, RX, K₂CO₃, dimethylformamide; iii, KOH, MeOH, H₂O.

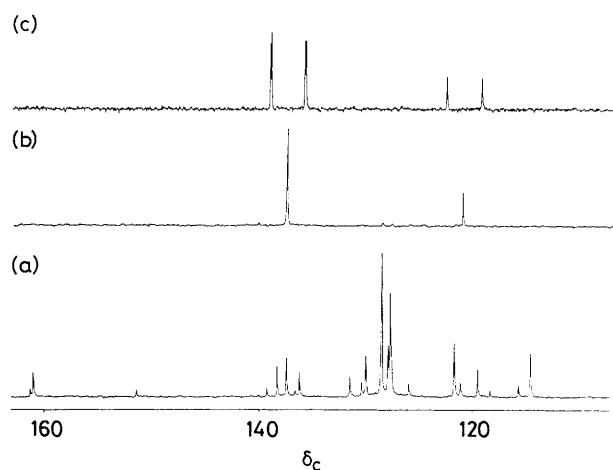
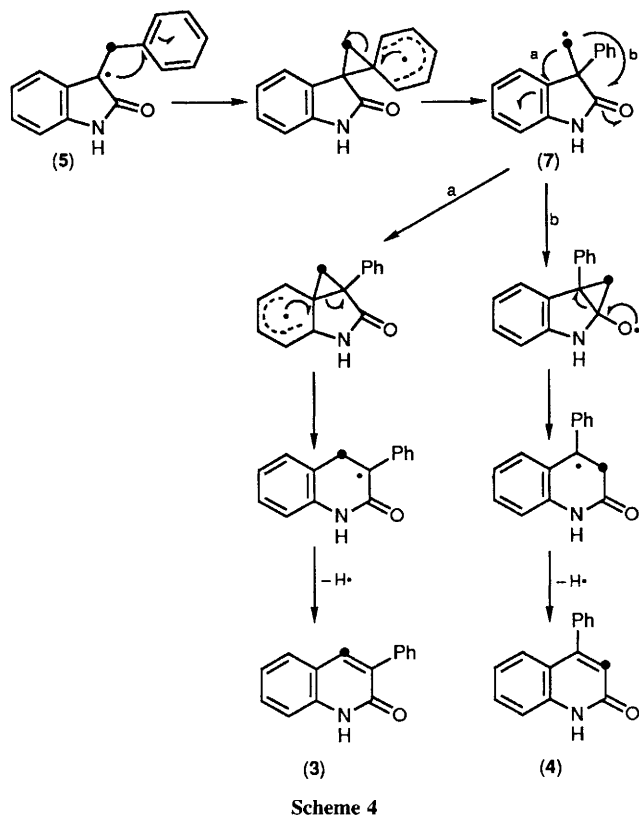
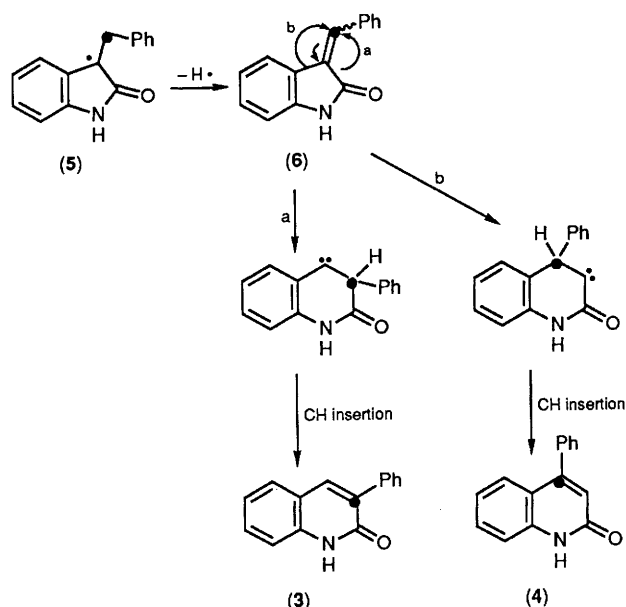
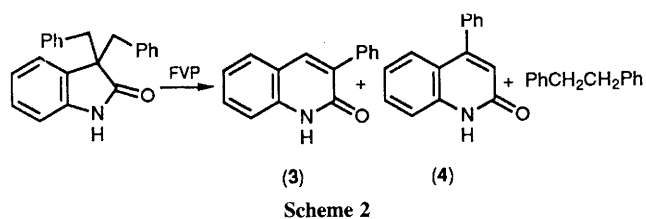
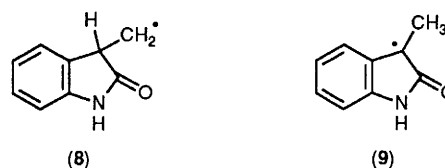


Figure 1. (a) ^{13}C NMR spectrum (CD_3SOCD_3) of (3) and (4) obtained from unlabelled precursor (1b); (b) ^{13}C NMR spectrum (CD_3SOCD_3) of (3) and (4) obtained from ^{13}C labelled precursor (1d); (c) as (b) (^1H -coupled version).



expansion and hydrogen atom cleavage steps. The first mechanism (Scheme 3) involves initial loss of a hydrogen atom to give the enone (6) which can give the two products by migration of the C(2)–C(3) bond (route a) or the C(3)–C(3a) bond (route b) followed by consolidation of the resulting carbenes. There is substantial precedent for such ring expansion in the pyrolytic behaviour of fulvenes.⁴ In the second possible mechanism (Scheme 4), the well known⁵ neophyl rearrangement is invoked to generate the 3-indolylmethyl radical (7). After this clearly endothermic step, the system can regain resonance energy either *via* a subsequent neophyl process (route a) or by interaction with the carbonyl group⁶ (route b) leading to the two products. The two possible mechanisms are clearly distinguishable by a ^{13}C labelling experiment (highlighted atoms in Schemes 3 and 4). The appropriate precursor (1d) was synthesised from [1- ^{13}C]benzyl chloride and the ^{13}C NMR spectra of the pyrolysates obtained from the labelled and unlabelled precursors are shown in Figure 1. It is clear that *one* carbon atom in each product is uniquely labelled (Figure 1b), and that this is a methine atom (Figure 1c), as required by the mechanism of Scheme 4. The ring expansion step therefore occurs by the free-radical pathway, proceeding *via* the neophyl rearrangement.

The situation with regard to the dimethyl derivative (1a) is less clear cut, though pyrolysis of the ^{13}C labelled material (1c) at 900 °C gave a mixture of 4-labelled and 3-labelled quinolinone (1.9:1.0) as expected of a mechanism involving a 3-indolylmethyl intermediate (8). Unfortunately, there is no low-energy route to this radical from the initial 3-methylindolyl species (9), since the required 1,2-H-shift is formally disallowed;⁷ however, preliminary cross-over experiments with deuteriated precursors do not exclude an intermolecular component to this pathway.

The results of this study have the wider synthetic implication that thermally generated free radicals adjacent to cyclic

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π -systems may undergo rearrangement processes leading to oxidative ring expansion, and further examples are under investigation. These gas-phase processes complement recent solution methods in which reductive ring expansion is observed.⁶

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References

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