Ring Expansion and Rearrangement Reactions of N-Heteroarylmethyl Radicals

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Flash vacuum pyrolysis of *N*-(*p*-chlorophenoxymethyl)azoles (*e.g.* **2** and **3**) gives ring expanded products (*e.g.* **4** and **8**) formed *via N*-heteroarylmethyl radicals (*e.g.* **1** and **6**); the mechanism of ring expansion generally involves a novel 'walk'-rearrangement of the radical centre.

There is considerable current interest in ring-expansion reactions of carbon-centred radicals, generated in solution under standard reductive conditions.¹ We describe here a gas-phase variant of these processes which leads to oxidative ring-expansion of *N*-heteroarylmethyl radicals 1 via novel 'walk' rearrangements of the intermediates.

The radicals **1** were generated (along with the *p*-chlorophenoxyl radical) by flash vacuum pyrolysis (FVP) of the corresponding *N*-(4-chlorophenoxy)methyl derivative **2** at 700 °C. The precursors **2**[†] were themselves obtained in *ca*. 60% yield by alkylation of the parent heterocycle using α ,4-dichloroanisole under basic conditions in dimethyl sulfoxide solution.² ¹³C-Labelled dichloroanisole was obtained by the method shown in Scheme 1.^{3,4}



Scheme 1 Reagents and conditions: i, ${}^{13}CH_3I$, K_2CO_3 , dimethylformamide; ii, PCl₅, heat



[†] All new compounds were characterised by their spectra and by elemental analysis.

FVP of the indolyl derivative **3** at 700–800 °C (10^{-2} Torr‡) gives rise to *p*-chlorophenol (90%) as expected, and to quinoline **4**, (66%) as the only ring-expanded product. No isoquinoline **5** could be detected. The expansion process is therefore initiated exclusively by attack of the *N*-indolyl-methyl radical **6** at the 2-position of the indole ring (Scheme 2 route a). Well-precedented attack at the 7a-position by a neophyl-type rearrangement^{5,6} (Scheme 2 route b) which would give rise to isoquinoline, clearly does not occur in this case. The mechanism was confirmed by pyrolysis of a ¹³C-labelled derivative (highlighted atoms in Scheme 2), and, as predicted, the majority of the label (>90%) is found at C-2 of the quinoline (¹³C NMR).

Although ring-expansion of the N-pyrrolylmethyl radical 7 similarly gives pyridine (8; 59%), the detailed mechanism of the rearrangement as revealed by the labelling experiment (¹³C NMR), differs significantly from the N-indolylmethyl



 $\ddagger 1 \text{ Torr} \approx 133 \text{ Pa}.$



case. Surprisingly, the label is distributed over all positions of the pyridine ring, with the majority located at the 3-position. This result may be explained by a 'walk'-rearrangement of the initial radical (Scheme 3).§ The occurrence of such a rearrangement is consistent with the results of an EPR study of the hydrocarbon analogue 9, in which exocyclic cleavage (bond p- leading to the 'walk') is known to be favoured over endocyclic cleavage (bond q- leading to ring expansion).8 In the pyrrolyl case, ring expansion by route c (Scheme 3) is apparently most favourable, and indeed it is known that drastic pyrolysis of N-alkylpyrroles under radical-chain conditions^{9,10} often gives 3-substituted pyridines as the major ring-expanded product.

§ A 1,5-shift of the N-substituent prior to radical formation could give a similar labelling pattern, but this is known to require much higher temperatures in our apparatus.7

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A similar mechanism via the relatively disfavoured orthoquinonoid intermediate 10 can explain residual label (<10%), found at the 3-position in the indolylmethyl experiment.

Ring expansion of the N-azolylmethyl radicals 11 and 12 produced contrasting results (Scheme 4). Thus the N-pyrazolylmethyl radical 11 expands regiospecifically to give pyrimidine 13 rather than pyridazine 14 and this is probably due to the cleavage of the particularly weak N-N bond of the diaziridinyl intermediate 15. These results confirm that 11 is a viable intermediate in the pyrolysis of dipyrazolylmethane,¹¹ from which pyrimidine has also been obtained. In contrast, the N-imidazolylmethyl radical 12 yields both pyrimidine 13 and pyrazine 16 in 3.7:1.0 ratio.

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