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Mechanism of Direct Side-chain Acylamination and Aminoarylation of 2- and 4-Picoline 1-Oxides

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Summary The isolation of radical coupling products and the observation of appropriate C.I.N.D.P. signals suggest that most of the title reactions proceed by homolysis of the anhydro-bases (4) or (9) followed by radical recombinations; a diaza-oxy-Cope rearrangement may still account for the formation of α -acylamination products.

TREATMENT of 2- and 4-picoline 1-oxides (and related compounds) with an N-arylbenzimidoyl chloride and a strong base leads to a mixture of side-chain acylaminated and acylaminoarylated products.¹ A diaza-oxy-Cope rearrangement (1) was initially suggested² as a possible explanation of the formation of (2), but the production of aminoarylated products (3) from 2-picolines and of similar products from 4-picolines required a reconsideration of the mechanism.

Heterolytic or homolytic cleavages of the anhydro-bases (4) and (9) and concerted intramolecular processes were considered. Attempts to trap an intermediate picolyl



cation³ were unsuccessful. Thus, when 2- or 4-picoline 1-oxide was treated with N-phenylbenzimidoyl chloride in the presence of triethylamine and m-dimethoxybenzene no picolyldimethoxybenzenes were formed.



Strong evidence for a radical pathway has now been obtained. Thus, when 2-benzylpyridine 1-oxide was boiled in (CH₂Cl)₂ with N-phenylbenzimidoyl chloride and triethylamine, $\alpha \alpha'$ -bis-(2-pyridyl)bibenzyl (5) † (38%) was obtained, in addition to N-(2-pyridylphenylmethyl)benzanilide (7) (40%) and benzanilide (36%). Analytically pure dimer (5) was separated into two components by h.p.l.c., undoubtedly corresponding to the threo- and erythro-diastereoisomers, but these were not collected and characterised further. Similarly, 2-ethylpyridine 1-oxide gave the dimer (6) (11%)and the expected (8) (17%). On the other hand, only p-(4-pyridylphenylmethyl)benzanilide (10) (44%) and benzanilide (27%) were isolated from 4-benzylpyridine 1-oxide, and no dimer or side-chain N-substituted product was observed.

Direct evidence for the formation of radical pairs in these reactions comes from the observation of the appropriate C.I.D.N.P. signals. When the reaction of 2-picoline 1-oxide



with N-phenylbenzimidoyl chloride in ethylene dichloride was carried out in an n.m.r. tube in the presence of Et_aN at room temperature, and the spectrum was monitored as a function of time, an emission singlet was observed at δ 4.05. Its intensity reached a maximum after ca. 95 s and then decayed to an apparent zero at 115 s, following which it grew into an absorption singlet corresponding to that of the α -CH₂ in p-(3). No C.I.D.N.P. signal was detected corresponding to radical coupling leading to α -acylamination (2) so that a concerted (diaza-oxy-Cope) process remains a possible pathway to this product.

When the reaction of 4-picoline 1-oxide with the imidoyl chloride and base at room temperature was monitored by n.m.r. two emission C.I.D.N.P. signals were observed at δ 5.1 and 3.9 with a lifetime of 90 and 120 s, respectively. The corresponding absorption singlets were found to be those of the γ -CH₂ in 4-(N-benzoyl-N-phenyl)picolylamine (12) and the γ -CH₂ in (11), respectively. Similarly, for the reaction of 4-benzylpyridine 1-oxide an emission C.I.D.N.P. singlet at δ 5.5 was observed, corresponding to the γ -methine proton in (10). No emission is expected for the formation of the dimer, if any is formed.



The results are most conveniently explained in terms of the homolysis of the N-O bond in the anhydro-bases (4) and (9) followed by radical coupling [with the proviso that (2) may rise in a concerted manner], as illustrated for (4) in the Scheme. As expected, α -C₅H₄NCHR (R = Ph, Me) are longer lived than the corresponding α -picolyl radical (R = H) thus permitting their dimerisation. It would appear as though coupling of γ-C₅H₄CHPh and PhCONPh is faster than dimerisation of the former.

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- [†] All new compounds gave satisfactory microanalytical and spectral data.
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