Direct Side-chain Acylamination of 4-Picoline 1-Oxides and Related Compounds

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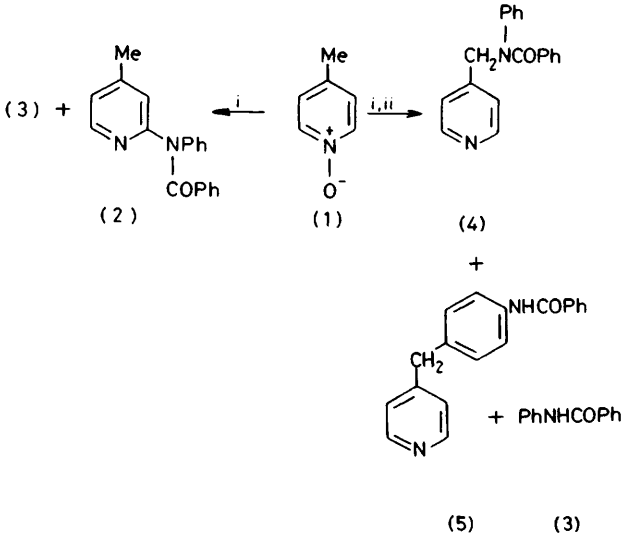
Summary The anhydro bases formed from the reaction of 4-picoline 1-oxides with *N*-substituted benzimidoyl chlorides and a strong base undergo a new molecular rearrangement to give mixtures of the side chain acylaminated (*e.g.* **4**) and acylaminoarylated products (*e.g.* **5**); 2-picoline 1-oxides behave similarly.

TREATMENT of 2-picoline 1-oxide with an imidoyl chloride in the presence of a base has been shown to give the side-chain acylaminated product.[1] A number of possible mechanisms for this reaction were considered including an aza-Cope rearrangement in the anhydro base. When an analogy is drawn between the nature of this product and those obtained in the reaction of picoline 1-oxides with acid anhydrides[2] it is then possible to expect a similar side-chain acylamination of 4-picoline derivatives. This is now shown to be the case.

Reaction of 4-picoline 1-oxide (**1**) with *N*-phenylbenzimidoyl chloride in ethylene chloride in the absence of other base yielded 2-*N*-benzoylanilino-4-picoline (**2**) and benzanilide (**3**).[3] When 1 equiv. of a strong tertiary base [DBU (DBU = 1,5-diazabicyclo[5·4·0]undec-5-ene) or preferably Et_3N] was added to the mixture (**2**) was not formed. Instead, a mixture of 4-(*N*-benzoyl-*N*-phenyl)picolylamine (**4**; 18%), m.p. 83—85 °C, *p*-(4-picolyl)benzanilide (**5**; 20%), m.p. 135—136 °C, and (**3**; 33%) was isolated (Scheme).†

An authentic sample of (**4**) was prepared from 4-chloromethylpyridine hydrochloride and aniline[4] followed by benzoylation, while an authentic sample of (**5**) was prepared by Sn–HCl reduction of 4-*p*-nitrobenzylpyridine followed by benzoylation.

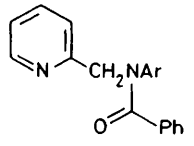


SCHEME. i, PhC(Cl)=NPh, $ClCH_2CH_2Cl$; ii, Et_3N

† All new compounds gave correct microanalytical and spectral data.

The isomeric compounds (**4**) and (**5**) and substituted derivatives thereof can be detected in solution by the characteristic n.m.r. absorptions of the corresponding methylene groups: that in (**4**) absorbs at δ 5·1 while that in (**5**) at δ 3·9.

2,4-Lutidine 1-oxide behaved similarly: acylamination in the absence of base gave the 6-*N*-benzoylanilino derivative (32·5%), m.p. 129—131 °C, whereas in the presence of base a mixture of at least five products was formed including products from the acylamination of either methyl group and the aminoarylation of either methyl group, together with benzanilide. Reaction of (**1**) with *N*-cyclohexylbenzimidoyl chloride in the presence of Et_3N gave only the expected *N*-benzyl-*N*-cyclohexyl-4-picolylamine as a yellow oil (32%) (picrate m.p. 168—170 °C)‡ together with benzanilide (36%).



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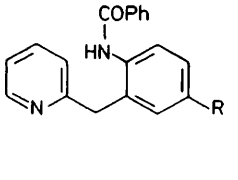

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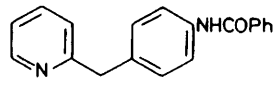
Ar = Ph; m.p. 81–83 °C; 38%
Ar = *p*-MeC_6H_4; m.p. 56–58 °C; 36%
Ar = *p*-$MeOC_6H_4$; m.p. 135–136 °C; 29%

R = H; m.p. 100–102 °C, 8%
R = Me; picrate m.p. 189–190 °C; 19%
R = OMe; oil; 18%

The isolation of products of side-chain aminoarylation (*e.g.* **5**) led us to re-examine the reaction with 2-picoline 1-oxide derivatives. Thus, reaction of 2-picoline 1-oxide with *N*-arylbenzimidoyl chlorides with an excess of Et_3N gave the side-chain acylaminated products (**6**) and the side-chain *ortho*-(**7**) and *para*- (if that position is vacant) (**8**) aminoarylated products. An authentic sample of (**8**) was prepared from 2-*p*-nitrobenzylpyridine 1-oxide[5] by reduction of both the nitro- and *N*-oxide functions with Fe–AcOH followed by benzoylation.



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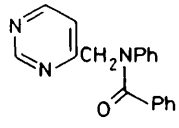
m.p. 141—142 °C; 19%

When *N*-cyclohexylbenzimidoyl chloride was used the side-chain acylaminated product was obtained (41%) as a yellow oil (picrate m.p. 168—169 °C). 4-Methylpyrimidine 3-oxide gave (**9**) (52%), m.p. 73—75 °C, and (**10**) (19%), m.p. 142—143·5 °C, together with benzanilide (13%). In the case of the 2-methyl derivatives the CH_2 group in (**6**) shows a ^1H n.m.r. absorption at δ 5·3 while that in (**7**) and (**8**) is at δ *ca.* 4·0.



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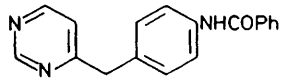

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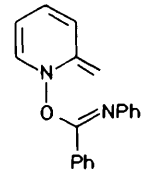

(11)

While formation of (**6**) [and (**4**)] could involve a concerted process, that of (**5**), (**7**), and (**8**) must involve either a homolytic or heterolytic cleavage of the N–O bond in the initial adduct anhydro base [(**11**) in the case of (**7**) and (**8**)].[2]

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‡ No *ortho*-isomer was detected in this case.

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