Tetrahedron Letters No.38, pp. 3371-3374, 1970. Pergamon Press. Printed in Great Britain.

ARYLATION-CARBOXYLATION OF PYRIDINE AND 4-PICOLINE[1]

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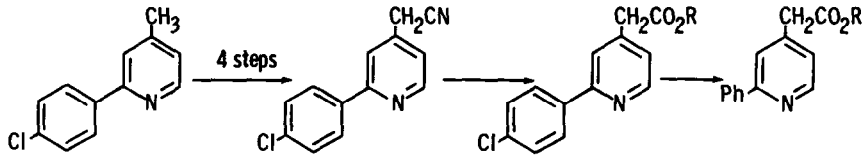
(Received in UK 15 July 1970; accepted for publication 19 July 1970)

The recent discovery, in these laboratories[2], that 2-p-chlorophenylthiazolyl-4-acetic possesses marked anti-inflammatory activity prompted us to investigate analagous arylpyridine acetic acids. At the beginning of this investigation, the only reported example of this group was 2-phenylpyridine-4-acetic acid, (1 R=H) which had been obtained in 16% yield by Prijs, Lutz and Erlenmeyer[3] by addition of phenyllithium to 4-picoline and carboxylation of the resultant intermediate. In view of the well-documented ready decarboxylation of pyridine 2- and 4-acetic acids[4], the reported melting point of the acid, 245-246°C, and the fact that it could be re-crystallised from ethanol without apparent loss seemed scarcely consistent with the structure claimed. We therefore undertook an unambiguous synthesis of 2-p-chlorophenylpyridine-4-acetic acid, to provide material, not only for biological evaluation, but also for conversion to authentic 2-phenylpyridine-4-acetic acid for direct comparison with the product obtained by the Swiss workers.



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The nitrile,3, was first prepared in 52% yield from the starting methyl compound, 4[5], in four steps: (i) glyoxylation with sodium hydride-diethyl oxalate in D.M.F.

(ii)conversion of the resultant α-keto ester to the α-oximino ester

(iii)base hydrolysis of the latter to the α-oximino acid

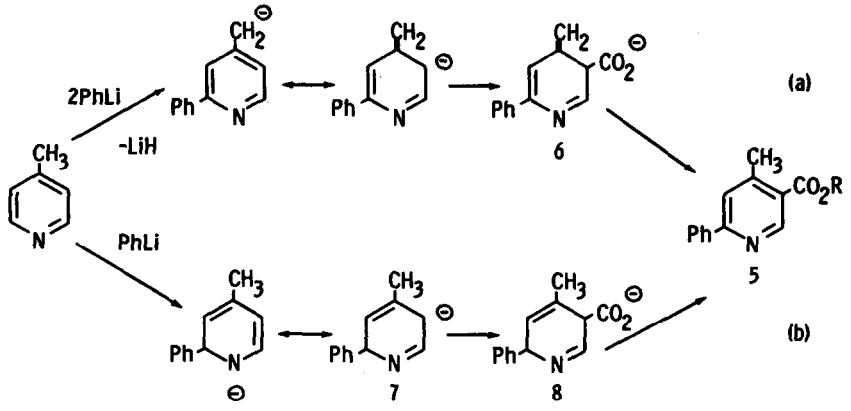
(iv)dehydration-decarboxylation of the α-oximino acid with acetic anhydride,

then transformed in quantitative yield to the corresponding ester, 2 ($R=CH_3$), by means of

methanol-sulphuric acid. Catalytic reduction of this material in the presence of one equivalent of triethylamine then smoothly afforded the phenyl analogue, 1 ($R=CH_3$). Although the N.m.r. spectrum was entirely consistent with this structure, the melting point 47-49°C (from petrol) suggested that this product differed from that (m.p. 79-81°C) assigned the same structure by the Swiss group. Furthermore base hydrolysis of the ester, 1, afforded authentic 2-phenylpyridine-4-acetic acid 1 (R=H) which after recrystallisation at 0°C melted at ca.90°C with visible decarboxylation[6], thus confirming our doubts about the structural assignment of the earlier workers[3].

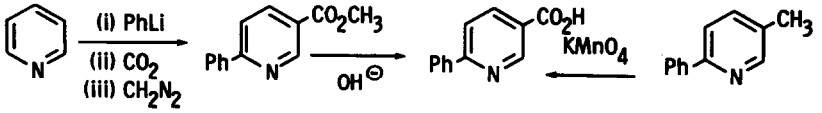
Repetition of their published procedure afforded the expected acid m.p. 243-246°C and its methyl ester m.p. 79-81°C. The N.m.r. spectrum of the latter showed not only the expected O-methyl resonance at 3.94, and an α-proton singlet at 9.16, but also a C-methyl singlet at 2.70, which could be accommodated only by the substituted nicotinic ester, 5 ($R=CH_3$).

In principle the acid 5(R=H) could result from two possible mechanisms:
(a) by successive additions of two moles of phenyllithium to 4-picoline, and carboxylation of the resulting ambident anion, 6 or (b) by carboxylation of the anion, 7, produced by addition of 1 mole of phenyllithium, and oxidation of the derived acid salt, 8, during work-up.



That the 4-methyl group need not be involved, and therefore that mechanism (b) obtained, was demonstrated simply by extending this reaction to pyridine itself. In this case carboxylation of the intermediate readily afforded a solid acid which was purified via chromatography of the derived methyl ester. The material thus obtained, (13% yield) consisted of pure methyl 2-phenyl-pyridine-5-carboxylate, 9, uncontaminated by any of the 2,3-isomer. Hydrolysis of the ester provided 2-phenylpyridine-5-carboxylic acid, 10, m.p. 231-233°C (lit.[7] m.p. 231-

232°C) identical in all respects to the product of permanganate oxidation of 5-methyl-2-phenyl-pyridine.



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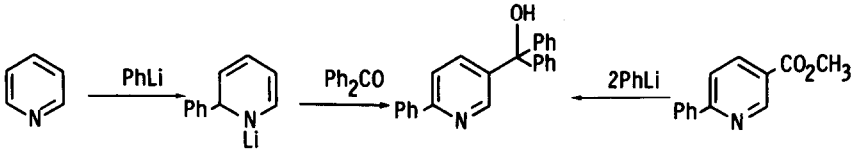
Although metallation of 4-picoline with phenyl-lithium with subsequent carboxylation has often been used[8] as a route to derivatives of pyridine-4-acetic acid, only the Swiss workers have reported products of arylation-carboxylation. However a search of the literature revealed that Abramovitch[9] had reported that treatment of pyridine with phenyllithium and subsequent addition of benzophenone gave up to 25% yield of a tertiary alcohol to which he had assigned the structure 11, on the basis of its N.m.r. spectrum and its non-identity with an authentic sample of the isomer 12. In view of the carboxylation results, it seemed more likely that this compound possessed the structure 13. This was readily confirmed by treatment of the ester, 9, with excess phenyllithium which afforded, in quantitative yield, the expected crystalline tertiary alcohol, 13, identical in all respects to that obtained by Abramovitch's procedure.



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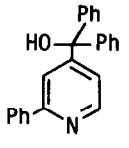

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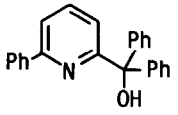

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More recently Giam and Stout[10] have isolated the intermediate 1-litho-2-phenyl-1,2-dihydro-pyridine, 14, formed by reaction of phenyllithium with pyridine, studied the alkylation of this material, and shown[11] that 2,5-disubstituted pyridines are obtained. In addition they showed

that such a two-stage procedure gave purer products in good yield than the corresponding one-step process. Thus our carboxylation studies complement this work and indicate the generality and potential of this approach to the hitherto inaccessible 2,5- di-substituted pyridines.

In an attempt to extend the scope of this phenylation-carboxylation procedure, we examined a number of substrates, but results were disappointing. Thus although 3-picoline afforded the expected 3-methyl-2-phenylpyridine-5-carboxylic acid, 16, in poor yield (cf.ref.7) no comparable product was obtained from 2-picoline (which clearly underwent only lateral metallation), 2,5-dimethylpyrazine, quinoline or isoquinoline.

References.

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6. The half life of this acid in 50% aqueous acetone was 143 minutes at 50° (cf. pyridine-4-acetic acid $t_{\frac{1}{2}}$=99 minutes at 50°).
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