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PYRIDINE ANNELATION OF o-METHYL ARYLCARBOXYLIC ACIDS WITH VILSMEIER REAGENTS

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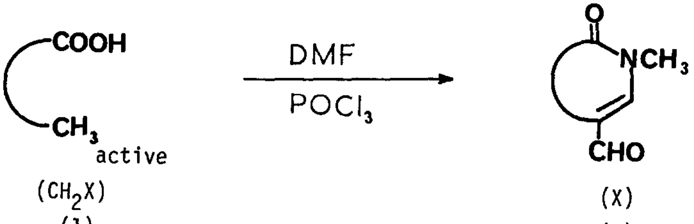
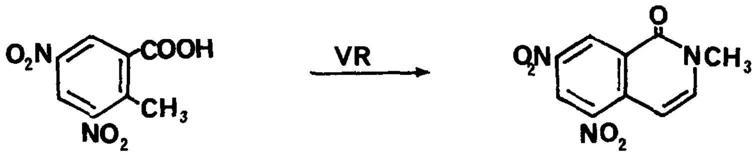
Summary: The annelation of a pyridine ring by its c-position to pyridines, quinolines- and quinoxalines bearing ortho methyl and carboxylic acid groups occurs on treatment with Vilsmeier reagents; the reaction incorporates the nitrogen of the reagent.

We wish to disclose our first endeavours in utilising a new synthetic route which should allow the synthesis of 5-, 6-, or 7-membered nitrogen heterocycles, exemplified in general in Scheme 1. The product (2) has incorporated nitrogen from the dimethylformamide, a process necessarily involving elimination of a methyl group.

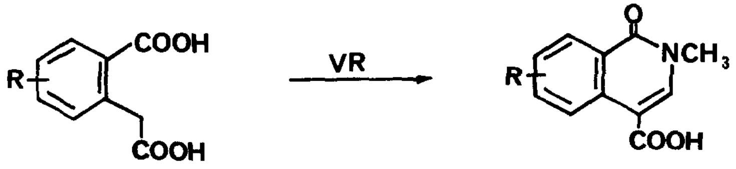


Scheme 1

The only previously reported analogues of this reaction are the unexpected conversion of 3,5-dinitro-o-toluic acid (3) into the isoquinolone[1] (4), a reaction which does not occur with the mono-nitro analogues[2], and the transformation of homophthalic acids (5) into isoquinolones[3] (6).

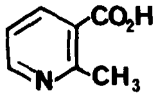


(3) (4)

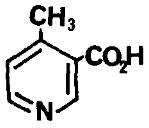


(5) (6)

A series of pyridines (**7–9**)^4, quinolines (**10a, b**)^5 and a quinoxaline(**10c**)^6 were next examined which satisfied the requirements of Scheme 1. In each case the Vilsmeier formylation with DMF and $POCl_3$ gave the product of type (2), i.e. compounds (**11–14**) respectively.



(7)



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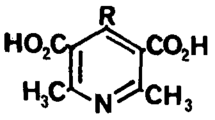
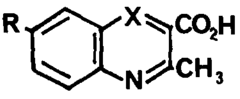


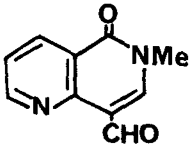
(9)

R=H, Ph or C_6H_4OMe-p

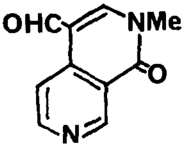


(10)

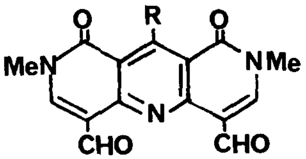
	X	R
a	CH	H
b	CH	OMe
c	N	H



(11) (47%)
m.p. 217°

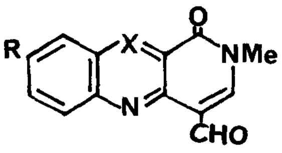


(12) (58%)
m.p. 254-6°



(13)

R	Yield	M.p.
H	18	339
Ph	27	346-9
C_6H_4OMe	15	194-5

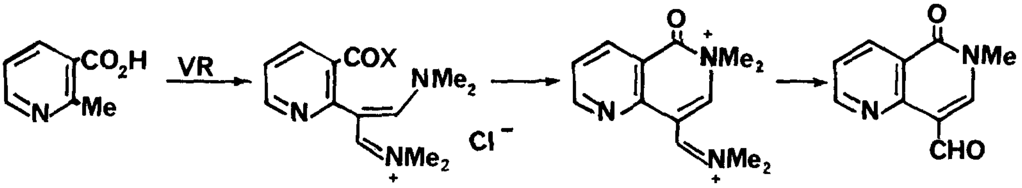


(14)

	R	X	Yield	M.p.
a	H	CH	48	285-6
b	MeO	CH	56	295-7
c	H	N	57	310-2

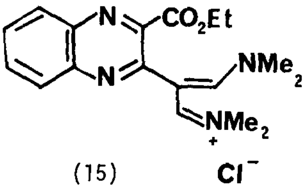
The lutidine dicarboxylic acids (**9**) underwent bis-cyclisation to yield the novel 2,5,8-anthyridines (**13**)[7]. A curious feature of some of these products (**11** and **14**) is their tendency to form complexes with alkali metal ions. Thus (**14b**) does not precipitate from an acidic solution on addition of sodium hydroxide while (**14a**) partially precipitates a sodium containing product. The quinoxaline derivative (**15c**) is an interesting deaza-alloxazine analogue.

We rationalise these transformations as shown in Scheme 2. It is surprising that the ethyl esters of the quinolines (**10a** & **b**) and pyridines (**9**) are unchanged by similar treatment. However from the quinoxaline (**10c**) was isolated the salt (**15**) by chloroform extraction of the hydrolysed reaction mixture, but the deaza-alloxazine (**16**) was obtained in good yield on work-up with ammonium hydroxide. Similarly the mono-ethyl-esters of the lutidines (**9**) gave the products (**17**).

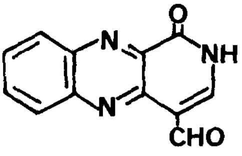


$X = OH, OPOCl_2$ or $OCH{=}\overset{+}{N}Me_2$

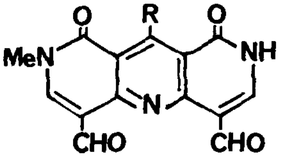
Scheme 2



(15)
m.p. 95-106°



(16)
m.p. 327-331°



(17)

R	Ph	C_6H_4OMe
Yield	37	47
M.p.	>350°	>350°

It would thus appear that a derivative of the acid such as the mixed carboxylic-phosphoric anhydride or the acyliminium salt (see Scheme 2) further activates the methyl group.

We are currently examining other examples of this curious and valuable synthesis.

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4. We thank Dr Don Berry of Reilly Tar Co. for a sample of (9) and Dr Barrington Cross of Cyanamid Corporation for a sample of (8).
5. Prepared by the method of D.R. Adams, J.N. Dominguez, and J.A. Perez, *Tetrahedron Letters,* 1983, 517.
6. Prepared according to the methods of C.H. Issidorides and M.J. Haddadin, *Tetrahedron Letters,* 1965, 3253; *J. Org. Chem.,* 1966, **31**, 4067; and of W. Dürckheimer, *Annalen,* 1972, **756**, 145.
7. We thank Mr G. Crosby and Dr J. Clark of Chemistry Department, Salford University, England for help with some preliminary studies of the formation of (13).

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