SYNTHESIS AND FUNCTIONALIZATION OF NEW PYRIDO [3,2-*f*] PYRROLO [1,2-*a*] [1,4] DIAZEPIN-5-ONES.

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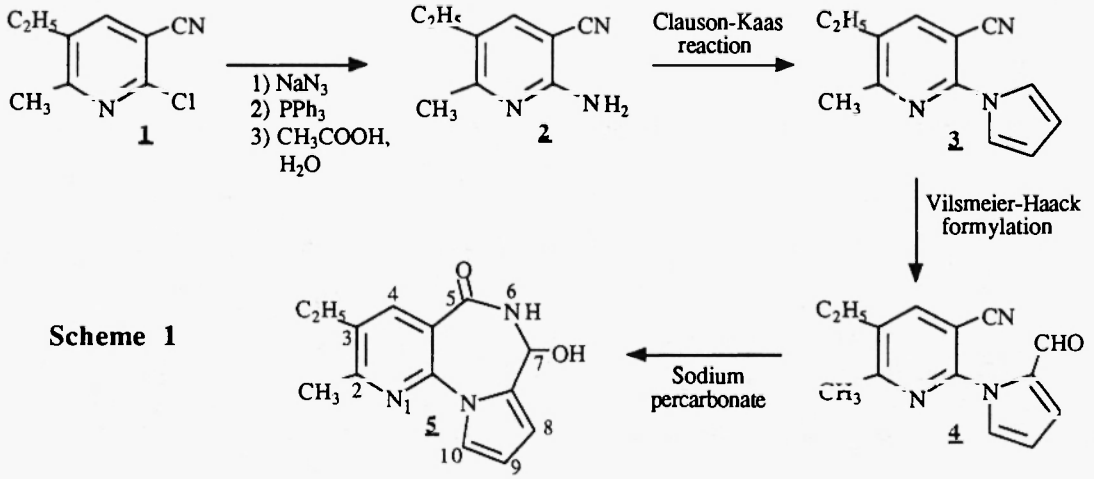
Abstract: Starting from the 2-chloro-5-ethyl-6-methylpyridine-3-carbonitrile **1**, we achieved the synthesis of new pyridine derivatives **4** and **5** whose appropriate treatments furnished new functionalized diazepine heterocycles.

Previous diazepines (TIBO, Nevirapine) (1) have shown antiviral activity against HIV-1. We describe here the access to new pyrido [3,2-*f*] pyrrolo [1,2-*a*] [1,4] diazepin-5-ones in one or two steps starting from 5-ethyl-6-methyl-2-[2-formyl(pyrrol-1-yl)] pyridin-3-carbonitrile **4**. This pathway, different from the one described by Korakas and Varvounis (2) leads to related structures. Structural data of the main compounds **3** to **9** appear in the table 1.

Pharmacological investigations about these compounds are in progress.

Paine has previously described the synthesis of the 2-chloro-5-ethyl-6-methylpyridin-3-carbonitrile **1** (3). The reaction of the latter successively with sodium azide, triphenyl phosphine then aqueous acetic acid (4) provides access to the 2-amino-5-ethyl-6-methylpyridine-3-carbonitrile **2** with an overall yield of 70%. This procedure was prefered to the one of Hoffman (5) that leads to the same compound in less favourable yield (20%).



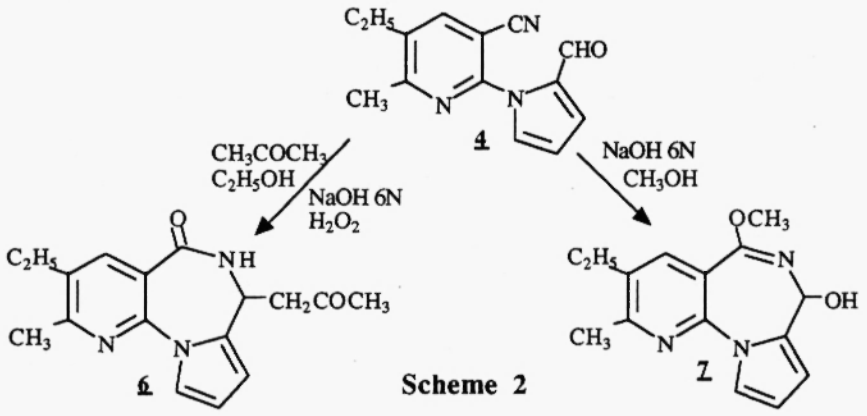
Scheme 1

The continuation of this synthetic route uses two classical methods: the Clauson-Kaas reaction (6) with 4-chloropyridine hydrochloride as a catalyst, providing the pyrrolyl derivative **3** (75%), then

Vilsmeier-Haack formylation leading to the compound **4** (73%).The treatment of compound **4** with sodium percarbonate (7) furnishes the new diazepine heterocycle **5** (38%).

As shown in the following schemes 2 and 3, both compounds **4** and **5** treated under suitable conditions are a good route to obtain various functionalized pyrido [3,2-*f*] pyrrolo[1,2 -*a*] [1,4] diazepinones.

Starting from the compound **4**, two types of reaction are employed (Scheme 2).

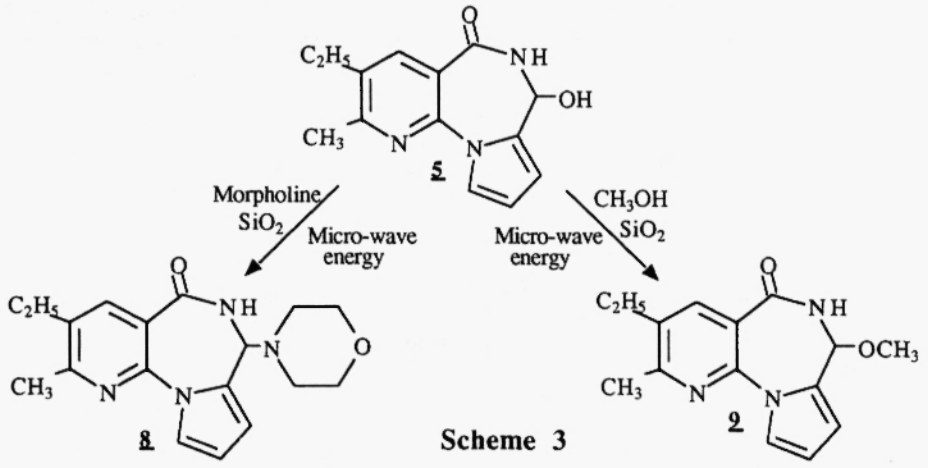


Scheme 2

Following a procedure described by Rault (8), the synthon **4** is subjected to a reaction with propanone. This procedure using ethanol as a solvent, sodium hydroxide and hydrogen peroxide provides access to the corresponding ketone **6** with a moderate yield (42%).

A second reaction allows obtaining the imino-ether **7** (63%), the starting material **4** being dissolved in methanol in the presence of aqueous sodium hydroxide and refluxed for 3 hours.

Similarly to the compound **4**, the heterocycle **5** is likely to furnish two series of functionalized diazepine heterocycles (scheme 3).



Scheme 3

The hydroxydiazepine **5** and an excess of morpholine or methanol is dissolved in acetonitrile. The mixture is then refluxed in a microwave oven in the presence of silicagel as a catalyst and the reaction is monitored by thin layer chromatography. This procedure furnishes the amine **8** (55%) and the ether **9** (67%).

TABLE 1

		^{1}H-NMR	
Compound	mp (°C)	δ (ppm) and multiplicity	solvent
3	63	1,25 (t, 3H); 2,56 (s, 3H); 2,65 (q, 2H) 6,36 (m, 2H); 7,67 (m, 2H); 7,72 (s, 1H)	$CDCl_3$
4	68	1,31 (t, 3H); 2,60 (s, 3H); 2,73 (q, 2H) 6,49 (dd, 1H); 7,18 (dd, 1H) 7,26 (dd, 1H) 7,82 (s, 1H); 9,64 (s, 1H)	$CDCl_3$
5	180	1,20 (t, 3H); 2,52 (s, 3H); 2,68 (q, 2H) 5,60 (d, 1H); 6,19 (d, 2H); 6,33 (d, 1H) 7,50 (s, 1H); 8,01 (s, 1H); 9,35 (d, 1H)	DMSO
6	182	1,30 (t, 3H); 2,22 (s, 3H); 2,38 (s, 3H) 2,71 (q, 2H); 3,11 (m, 2H); 4,90 (m, 1H) 6,00 (m, 1H); 6,24 (m, 1H) 7,53 (m, 1H); 8,08 ((s, 1H); 8,12 (s, 1H)	$CDCl_3$
7	156	1,28 (t, 3H); 2,59 (s, 3H); 2,69 (q, 2H) 3,33 (d, 1H); 3,80 (s, 3H); 5,59 (d, 1H) 6,18 (m, 1H); 6,26 (dd, 1H) 7,28(dd, 1H); 7,81 (s, 1H)	$CDCl_3$
8	184	1,30 (t, 3H); 2,10 (m, 2H); 2,55 (m, 2H) 2,60 (s, 3H); 2,70 (q, 2H); 3,36 (t, 4H) 4,47 (d, 1H); 6,20 (dd, 1H) 6,26 (dd, 1H); 7,60 (dd, 1H) 7,95 (d, 1H); 8,05 (s, 1H)	$CDCl_3$
9	175	1,29 (t, 3H); 2,56 (s, 3H); 2,69 (q, 2H) 3,20 (s, 3H); 5,28 (d, 1H); 6,27 (d, 2H) 7,69 (s, 1H); 8,15 (s, 1H); 8,35 (d, 1H)	$CDCl_3$

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