BASE-PROMOTED ISOMERIZATION OF 4-(PYRROLYLMETHYL)-1,2,3,6-TETRAHYDROPYRIDINES[1]

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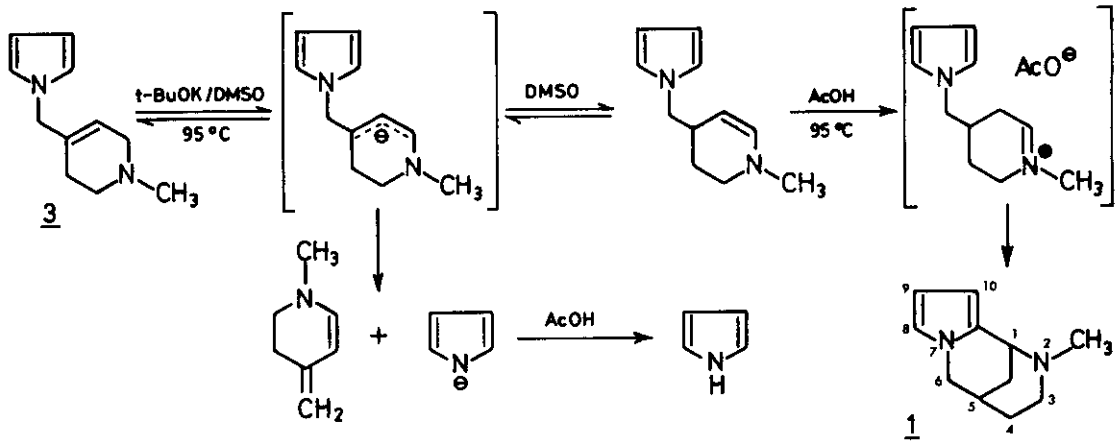
Abstract – The base-promoted isomerization followed by acetic acid treatment of two 4-(pyrrolylmethyl)-1,2,3,6-tetrahydropyridines is studied. 1-Methyl-4-(1-pyrrolylmethyl)-1,2,3,6-tetrahydropyridine (3) gave a mixture of the methanopyrrolodiazocine 1 and pyrrole, the latter arising from a fragmentation reaction. 1-Methyl-4-(1-methyl-2-pyrrolylmethyl)-1,2,3,6-tetrahydropyridine (4) afforded a mixture of recovered tetrahydropyridine and a 4-methylenepiperidine 5 instead of the cyclization product 2.

In connection with our synthetic studies on methanopyrroloazocines[2] and methanopyrrolodiazocines[3], bridged tricyclic systems containing a pyrrole ring, we intended to study if the base-promoted isomerization of 4-(pyrrolylmethyl)-1,2,3,6-tetrahydropyridines (3-piperideines) into the corresponding 1,2,3,4-tetrahydropyridines (enamines) followed by treatment with acid was a suitable method for the preparation of hexahydro-1,5-methanopyrrolo[1,2-a][1,4]diazocine 1 and hexahydro-4,8-methanopyrrolo[3,2-c]azocine 2 systems. Compounds 1 and 2 can be considered as pyrrole analogues of the fundamental cyclic framework of the indole alkaloids vinoxine[4] and dasycarpidone[5].

The procedure has been applied in some instances to the synthesis of indole alkaloids[6-12] (especially when the tetrahydropyridine ring has substituents such as 4-acyl or 6-aryl which acidify the C_6 proton and thus facilitate the isomerization), although there are no precedents of its use in the synthesis of polycyclic pyrrole systems. The isomerization of 3-piperideines to the thermodinamically more stable[6] 2-piperideines occurs *via* an allylic carbanion generated by treatment with potassium *tert*-butoxide in dimethyl sulfoxide at 95°C, and the cyclization upon the aromatic ring takes place *via* a 2,3,4,5-tetrahydropyridinium salt resulting from protonation of the 2-piperideine in acetic medium[6].

Both 4-(pyrrolylmethyl)-1,2,3,6-tetrahydropyridines 3 and 4 required in our case were prepared from 4-cyanopyridine. The former[13] was synthesized by lithium aluminum hydride reduction of 4-cyanopyridine to 4-aminomethylpyridine, followed by the Clauson-Kaas reaction with 2,5-diethoxytetrahydrofuran, quaternization of the pyridine nitrogen atom and sodium borohydride reduction of the resulting pyridinium salt. The tetrahydropyridine 4[14] was obtained by the Houben-Hoesch reaction between 4-cyanopyridine and 1-methylpyrrole, subsequent Wolff-Kishner reduction of the resulting pyridyl pyrrolyl ketone, quaternization and borohydride reduction[15].

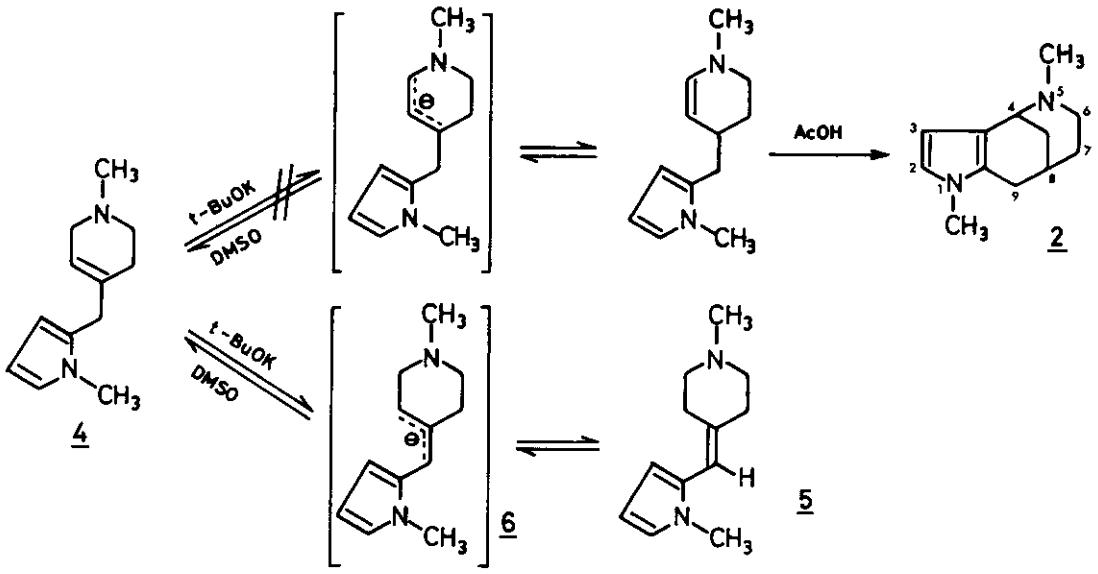
The potassium tert-butoxide (freshly sublimed) treatment of the tetrahydropyridine 3 in deoxygenated dimethyl sulfoxide at 95°C for 20 hours followed by the addition of excess 50 % deoxygenated acetic acid and heating at 95°C for 1 hour gave the methanopyrrolodiazocine 1 in 9 % yield[16]. When the reaction times were shortened to 6 hours and 5 minutes, respectively, a mixture of the methanopyrrolodiazocine 1 (25 % yield) and pyrrole (30 % yield) was obtained. Further reduction of the reaction times did not result in any improvement.



The formation of pyrrole is interpreted by considering that the initially formed allylic carbanion can undergo a fragmentation reaction leading to 1-pyrrolyl anion and a dienamine which polymerizes in the final acid treatment.

On the other hand, the exposure of the tetrahydropyridine 4 to potassium tert-butoxide in dimethyl sulfoxide at 95°C for 6 hours, followed by treatment with 50 % acetic acid at 95°C for 3 minutes yielded a 4:5 mixture (ratio calculated by nmr) of the starting tetrahydropyridine and 1-methyl-[(1-methyl-2-pyrrolyl)methylene]piperidine (5)[17], respectively. The ir spectrum ($CHCl_3$) of 5 showed an absorption at 1690 cm^{-1} due to the double bond conjugated with the pyrrole ring. Its nmr spectrum (CCl_4) showed signals for one α-pyrrole proton (δ 6.30) and for two β-pyrrole pro-

tons (δ 5.85), thus indicating that 5 was not a cyclization product. The vinylic proton resonated at δ 5.85, together with the β-pyrrole protons, although it was shifted at δ 6.22 by the addition of trifluoroacetic acid.



The above result appeared to show that, as a consequence of the acidity of the interannular methylene protons in the starting tetrahydropyridine 4, the initial deprotonation occurs at this position affording the conjugated anion 6, thus precluding the formation of the enamine required for cyclization. Reprotonation of 6 can take place either at the C_3 position of the piperidine ring affording the 4-methylenepiperidine 5 or at the interannular carbon atom thus regenerating the starting tetrahydropyridine 4.

The reported results put in evidence limitations of the base-promoted isomerization of 3-piperideines into 2-piperideines when there is a pyrrolylmethyl substituent at the 4-position of the tetrahydropyridine ring. The fragmentation observed in the first case can be related to that reported on a 4-(hydroxyalkyl) substituted 3-piperideine[9].

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REFERENCES AND NOTES.

1. This work was presented in a preliminary form at the 12th International Symposyum on the Chemistry of Natural Products, Tenerife, 1980.

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13. Picrate, mp 156-158°C (ethanol); nmr (CCl_4): 1.86 (m,2H,C^3H_2); 2.18 (s,3H,NCH_3); 2.30 (dd,2H,C^2H_2); 2.78 (bs,2H,C^6H_2); 4.18 (s,2H,interannular CH_2); 5.31 (bs, 1H,=CH); 5.93 (t,J=2.4 Hz,2H,pyrrole-H_β); 6.40 (t,J=2.4 Hz,2H,pyrrole-H_α).

14. Picrate, mp 178-180°C (ethanol); nmr (CCl_4): 2.0 (m,2H,C^3H_2); 2.18 (s,3H,NCH_3); 2.36 (dd,2H,C^2H_2); 2.76 (m,2H,C^6H_2); 3.17 (bs,2H,interannular CH_2); 3.42 (s,3H, pyrrole-NCH_3); 5.17 (bs,1H,=CH); 5.75 (m,2H,pyrrole-H_β); 6.28 (m,1H,pyrrole-H_α).

15. All products gave satisfactory elemental analysis.

16. Picrate, mp 188-190°C (ethanol); nmr (CCl_4): 1.2-2.4 (m,7H alicyclic); 2.02 (s,3H,NCH_3); 3.3-4.2 (m,3H,C^6H_2 and C^1H); 5.64 (m,1H,$C^{10}H$); 5.90 (m,1H,C^9H); 6.38 (m,1H,C^8H).

17. Picrate, mp 159-161°C (ethanol); nmr (CCl_4): 2.18 (s,3H,NCH_3); 2.32 (bs,8H, piperidine); 3.41 (s,3H,pyrrole-NCH_3); 5.85 (m,3H,pyrrole-H_β and =CH); 6.30 (m,1H,pyrrole-H_α).

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