ADDICTION OF INDOLES TO N-ALKYLPIRIDINIUM SALTS. SYNTHESIS OF (DIHYDROPYRIDYL)INDOLES

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Abstract—The addition of the sodium salt of several indole derivatives 1 to N-alkylpyridinium salts 2 having an electron-withdrawing substituent at the 3-position is studied.

The addition of stabilized carbon nucleophiles to N-alkylpyridinium salts has proved to be a useful synthetic tool, especially in the field of indole alkaloids.1 Thus, we recently reported2 that interaction of the enolates derived from 1a or 1b (LDA, THF, -78 to -30 °C, 2 h) with pyridinium salts 2a or 2b, followed by acidic cyclization of the resulting 1,4-dihydropyridine afforded the corresponding tetracycles 3a-c. These compounds possess four of the five rings of pentacyclic Stychnos alkaloids.3
A different result was produced when the reaction conditions of the first step were modified. Thus, when the reaction of the ester 1a with pyridinium salt 2a was carried out in methanolic solution in the presence of sodium methoxide as the base, a yellow compound, which remained unchanged after acidic treatment, precipitated (60% yield) from the reaction mixture. On the basis of its $^1$H-nmr spectrum and elemental analysis, it was tentatively assigned as the 3-(dihydropyridyl)indole 4a.

However, further careful examination of the $^{13}$C-nmr data of this dihydropyridine indicated that C-2 of the dihydropyridine ring was the site of attachment to the indole nucleus. Therefore, the correct structure of this 3-(dihydropyridyl)indole is that depicted in 5a.

![Figure 1. Two-dimensional nmr spectrum (HETCOR) of 5a (d$_6$-DMSO)](image-url)
The $^1\text{H} - ^{13}\text{C}$ heterocorrelated nmr spectrum of 5a as well as the signal assignment is showed in the Figure 1. The above data make evident the presence of a 2,3-disubstituted indole ring, a methoxycarbonylimethyl unit, and a doubly vinylogous urethane moiety. The nmr chemical shift ($\delta$ 55.2) of the sp$^3$-hybridized dihydropyridine carbon is in agreement with that expected for a 2-(3-indolyl)-1,2-dihydropyridine and quite different from those observed in 4-(3-indolyl)-1,4-dihydropyridines.\(^7\)

Formation of 1,2-dihydropyridine 5a can be rationalized by considering a kinetic attack by C-3 of the indolyl anion at the a-position of the pyridinium salt followed by irreversible aromatization. To our knowledge there are no precedents of nucleophilic additions of indoles to \(N\)-alkylpyridinium salts.\(^8\)

The above reaction seems to be quite general and of preparative interest. Thus, treatment\(^6\) of indole (1c) and 2-methylindole (1d) with sodium methoxide and then with the pyridinium salt 2a afforded the corresponding 1,2-dihydropyridines 5b\(^9\) and 5c\(^10\) in 50 and 80 % yield, respectively. In a similar manner 2-methylindole (1d) reacted with other pyridinium salts (2c\(^11\), 2d\(^12\)) having an electron-withdrawing substituent (formyl or acetyl) at the 3-position to give the corresponding 3-(1,2-dihydro-2-pyridyl)indoles 5d\(^10\) and 5e\(^10\) (26 and 95 % yield, respectively), although in the first case the 3-(1,4-dihydro-4-pyridyl)indole 4d\(^10\) was also isolated in 13 % yield.\(^13\) The most noteworthy $^1\text{H}$- and $^{13}\text{C}$-nmr data of 3-(dihydropyridyl)indoles 4 and 5 are showed in Table 1.

As could be expected, two requisites for the success of the reaction are the presence of an electron-withdrawing substituent at the 3-position of the pyridinium salt and the absence of substituent at the indole nitrogen. According with this, 2-methylindole (1d) failed to react with pyridinium salt 2e under the usual reaction conditions\(^6\) and, similarly, the indole derivative 1b was unreactive to the pyridinium salt 2a.

Finally, condensation\(^6\) of the sodium salt of 3-methylindole with pyridinium salt 2a gave in 51 % yield 1-(1,4-dihydro-4-pyridyl)indole 6\(^10\) as a sole isolable product.\(^14\) The structure of 6 was deduced from its nmr data (see Table 1), especially from the $^1\text{H}$-nmr chemical shift ($\delta$ 2.17) of the methyl group at the indole 3-position and the $^{13}\text{C}$-nmr chemical shift ($\delta$ 47.4) of the sp$^3$-hybridized dihydropyridine carbon. Formation of 1,4-dihydropyridine 6 can be explained taking into account that, in this case, the attack of the indolyl anion, either by C-3 or by the nitrogen, to the pyridinium salt is reversible and, consequently, leads to the thermodynamically more stable product, i.e. a 1,4-dihydro-
### Table 1. $^1$H- and $^{13}$C-Nmr Data of (Dihydropyridyl)indoles 4-6$^a$-c

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<th>H-5</th>
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$^a$In ppm relative to TMS. Measured in CDCl$_3$ solution at 200 MHz ($^1$H-nmr) or 50.3 MHz ($^{13}$C-nmr). $^b$Values in parentheses are coupling constants in Hz. $^c$The $^{13}$C-nmr assignments are in agreement with off-resonance spectra. $^d$Data from the spectrum of a 4b+5b mixture. $^e$Measured in d$_6$-DMSO. $^f$Signal at 6.68 in CDCl$_3$. $^g$The assignment may be interchanged. $^h$Measured in CDCl$_3$-d$_6$-DMSO. $^i$R$_1$:CH$_3$; R$_2$:CH=CH-CO$_2$CH$_3$. 
pyridine in which the γ-substituent is 3-methyl-1-indolyl rather than 3-methyl-3H-indol-3-yl. 15

The reaction here reported constitutes a useful synthetic entry to 3-(2-piperidinyl)indoles, 16 a structural unit present in a large number of indole alkaloids. Thus, catalytic hydrogenation (Pd-C) of 1,2-dihydropyridine 5c afforded the corresponding piperidine 7 in nearly quantitative yield. 17

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. For a review, see: M.-L. Bennasar, R. Lavilla, M. Alvarez, and J. Bosch, Heterocycles, 1988, 27, 789.
6. The general procedure was: 1) generation of the sodium salt by treatment of the indole derivative 1 with sodium methoxide in methanol at 0 °C for 30
min, ii) addition of pyridinium salt 2 at this temperature, and iii) stirring at room temperature for 6-16 h.


9. Minor amounts of 1,4-dihydropyridine 4b were detected by ¹H-nmr from the crude reaction mixture.

10. This compound gave elemental analysis consistent with the proposed structure.


13. Formation of 1,4-dihydropyridine 4d probably reflects the higher reactivity of the γ-position of the pyridinium salt when the B-substituent is formyl.

14. Minor amounts of the corresponding 1,2-dihydropyridine were detected by nmr from the crude reaction mixture.

15. The reversibility of the nucleophilic attack was evident from the tendency of 1,4-dihydropyridine 6 to undergo fragmentation into the starting materials: i) all attempts to purify 6 by crystallization or column chromatography resulted in the formation of 3-methylindole and the pyridinium salt 2a, and ii) reduction of 6 with sodium borohydride in methanol gave 3-methylindole and a mixture of methyl (E)-1-methylyopyridine-3-acrylates.


17. 7: ¹H-nmr (CDCl₃, δ) 1.93 (s, 3 H, CH₃), 2.19 (dd, J=12, 3.2 Hz, 1H, H-6ax), 2.33 (s, 3 H, NCH₃), 2.87 (ddd, J=12, 1.8, and 1.8 Hz, 1 H, H-6eq), 3.03 (dd, J=9.2 and 2.9, 1 H, H-2ax), 3.68 (s, 3 H, OCH₃), 6.99-7.21 (m, 3 H, ArH), 7.79-7.86 (m, 1 H, ArH), 7.96 (s, 1 H, NH). The picrate melt at 158-160 °C (acetone-ether).

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