

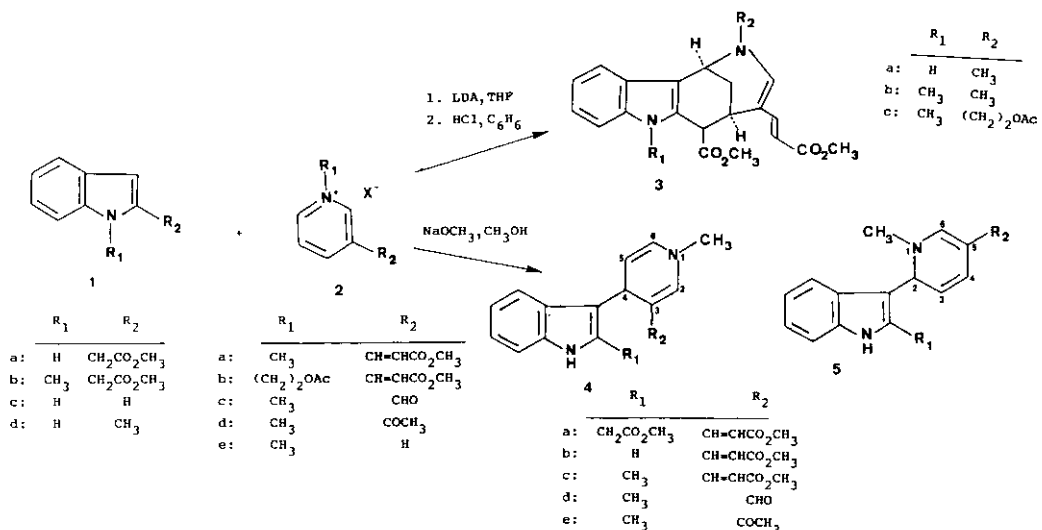
ADDITION OF INDOLES TO *N*-ALKYLPYRIDINIUM SALTS. SYNTHESIS OF (DIHYDROPYRIDYL)INDOLES

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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 β-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 *Strychnos* 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**⁴ with pyridinium salt **2a**⁵ was carried out in methanolic solution in the presence of sodium methoxide as the base,⁶ a yellow compound, which remained unchanged after acidic treatment, precipitated (60 % yield) from the reaction mixture. On the basis of its ¹H-nmr spectrum and elemental analysis, it was tentatively assigned¹ as the 3-(dihydropyridyl)indole **4a**.

However, further careful examination of the ¹³C-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**.

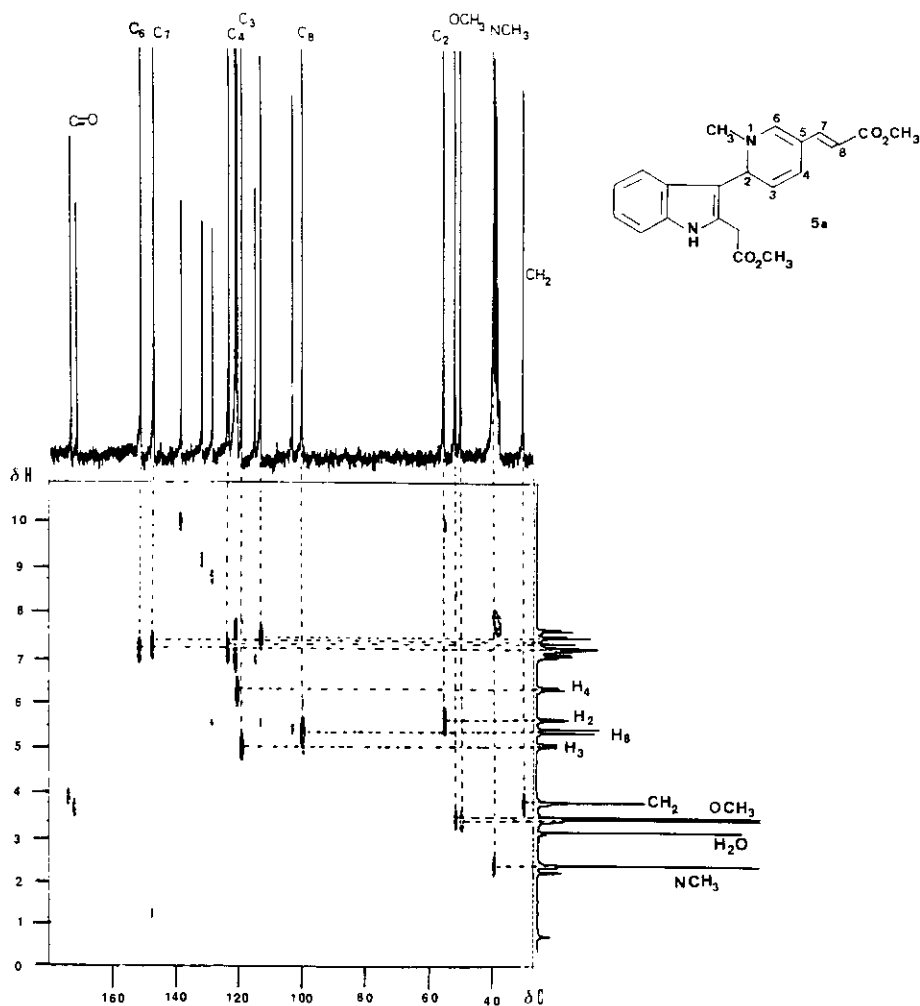


Figure 1. Two-dimensional nmr spectrum (HETCOR) of **5a** (d_6 -DMSO)

The ^1H - ^{13}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 methoxycarbonylmethyl unit, and a doubly vinylogous urethane moiety. The nmr chemical shift (δ 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 α -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, treatment⁶ 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 ^1H - and ^{13}C -nmr data of 3-(dihydropyridyl)indoles **4** and **5** are showed in Table 1.

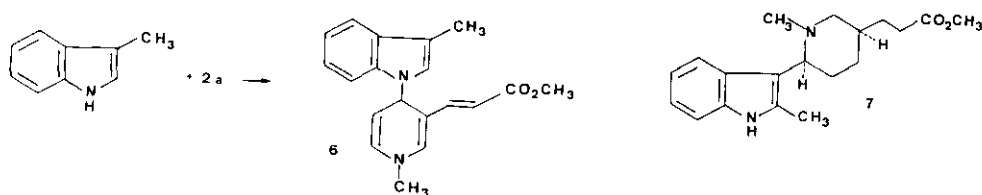
As could be expected, two requisites for the success of the reaction are the presence of an electron-withdrawing substituent at the 3-position of the pyridinium salt and the absence of substituent at the indole nitrogen. According with this, 2-methylindole (**1d**) failed to react with pyridinium salt **2e** under the usual reaction conditions⁶ and, similarly, the indole derivative **1b** was unreactive to the pyridinium salt **2a**.

Finally, condensation⁶ 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 ^1H -nmr chemical shift (δ 2.17) of the methyl group at the indole 3-position and the ^{13}C -nmr chemical shift (δ 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. ¹H- and ¹³C-Nmr Data of (Dihydropyridyl)indoles 4-6^{a-c}

¹ H-Nmr: 13-C-Nmr:	H-2 C-2	H-3 C-3	H-4 C-4	H-5 C-5	H-6 C-6	NCH ₃	R ₁	R ₂
4b^d	6.48 d (1.2)	----	4.80 d (6.0)	4.95 dd (8.4, 6.0)	5.80 dm (8.4)	3.15 s	----	3.59 s
4d	6.85 d (1.6) 149.0	----	4.79 dt (4.8, 1.2) 26.2	5.00 ddd (7.8, 4.8, 0.8) 109.1	5.94 ddd (7.8, 1.6, 1.2) 127.1	3.31 s 40.7	2.45 s 11.2	8.90 br s 187.6
5a^e	5.62 dd (3.6, 2.0) 55.2	5.09 dd (10.0, 3.6) 116.9	6.25 dt (10.0, 2.0) 118.4	----	7.09 ^f d (2.0) 148.2	2.64 s 40.0	3.62 ^g s, 3.92 s 170, 51.8 ^g , 31.2	3.57 ^g s, 5.39 d, 7.15 d (16.0) (16.0)
5b	5.46 dd (3.8, 1.2) 57.1	5.27 dd (10.0, 3.8) 117.2	6.29 dt (10.0, 1.2) 119.5	----	6.53 d (1.2) 146.4	2.77 s 41.2	----	3.73 s, 5.55 d, 7.25 d (15.0) (15.0)
5c	5.58 dd (3.8, 1.2) 54.7 ^e	5.18 dd (9.6, 3.8) 116.4	6.27 dt (9.6, 1.2) 118.0	----	6.57 d (1.2) 147.6	2.69 s 39.4	2.42 s 10.5	3.72 s, 5.53 d, 7.25 d (14.7) (14.7)
5d	5.67 dd (3.5, 1.9) 57.9 ^h	5.20 dd (10.2, 3.5) 116.0	6.58 ddd (10.2, 1.9, 0.6) 118.9	----	7.38 d (0.6) 155.6	2.88 s 41.0	2.46 s 11.3	8.72 br s 182.3
5e	5.55 dd (3.6, 1.8) 55.9	5.01 dd (10.1, 3.6) 114.2	6.56 br d (10.1) 118.3	----	7.41 br s (10.1) 109.5	2.77 s 40.8	2.42 s 11.3	2.20 s 190.0, 23.8
6^{e,i}	6.95 d (2.6) 145.7	----	6.11 d (4.4) 47.4	4.94 dd (7.8, 4.4) 109.5	6.40 br d (7.8) 130.4	3.27 s 40.8	2.17 s 9.6	3.47 s, 5.24 d, 7.28 d (15.4) (15.4)

^aIn ppm relative to TMS. Measured in CDCl₃ solution at 200 MHz (¹H-nmr) or 50.3 MHz (¹³C-nmr). ^bValues in parentheses are coupling constants in Hz. ^cThe ¹³C-nmr assignments are in agreement with off-resonance spectra. ^dData from the spectrum of a 4b+5b mixture. ^eMeasured in d₆-DMSO. ^fSignal at δ 6.68 in CDCl₃. ^gThe assignment may be interchanged. ^hMeasured in CDCl₃-d₆-DMSO. ⁱR₁:CH₃; R₂:CH=CH-CO₂CH₃



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-piperidyl)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

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- min, ii) addition of pyridinium salt **2** at this temperature, and iii) stirring at room temperature for 6–16 h.
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 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.
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 13. Formation of 1,4-dihydropyridine **4d** probably reflects the higher reactivity of the γ -position of the pyridinium salt when the β -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 (ϵ)-1-methyltetrahydropyridine-3-acrylates.
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 17. ¹H-nmr (CDCl₃, δ) 1.93 (s, 3 H, CH₃), 2.19 (dd, J=12, 3.2 Hz, 1 H, 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 picrate¹⁰ melted at 158–160 °C (acetone-ether).

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