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

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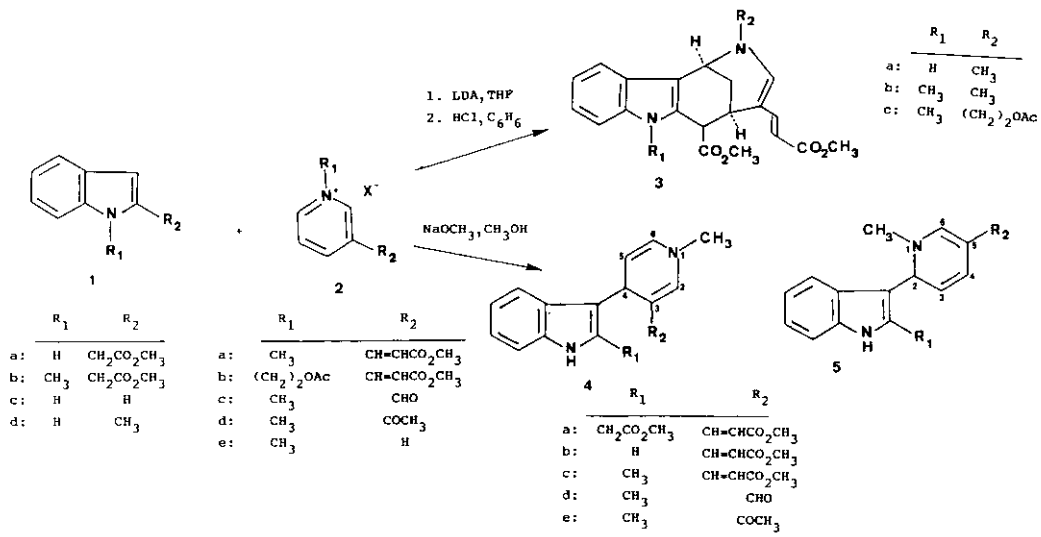
Abstract- The addition of the sodium salt of several indole derivatives 1 to *N*-alkylpyridinium salts 2 having an electron-withdrawing substituent at the ß-position is studied.

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 reported[2] 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]



	R_1	R_2
a:	H	$CH_2CO_2CH_3$
b:	CH_3	$CH_2CO_2CH_3$
c:	H	H
d:	H	CH_3

	R_1	R_2
a:	CH_3	$CH{=}CHCO_2CH_3$
b:	$(CH_2)_2OAc$	$CH{=}CHCO_2CH_3$
c:	CH_3	CHO
d:	CH_3	$COCH_3$
e:	CH_3	H

	R_1	R_2
a:	H	CH_3
b:	CH_3	CH_3
c:	CH_3	$(CH_2)_2OAc$

	R_1	R_2
a:	$CH_2CO_2CH_3$	$CH{=}CHCO_2CH_3$
b:	H	$CH{=}CHCO_2CH_3$
c:	CH_3	$CH{=}CHCO_2CH_3$
d:	CH_3	CHO
e:	CH_3	$COCH_3$

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 ^{1}H-nmr spectrum and elemental analysis, it was tentatively assigned[1] 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**.

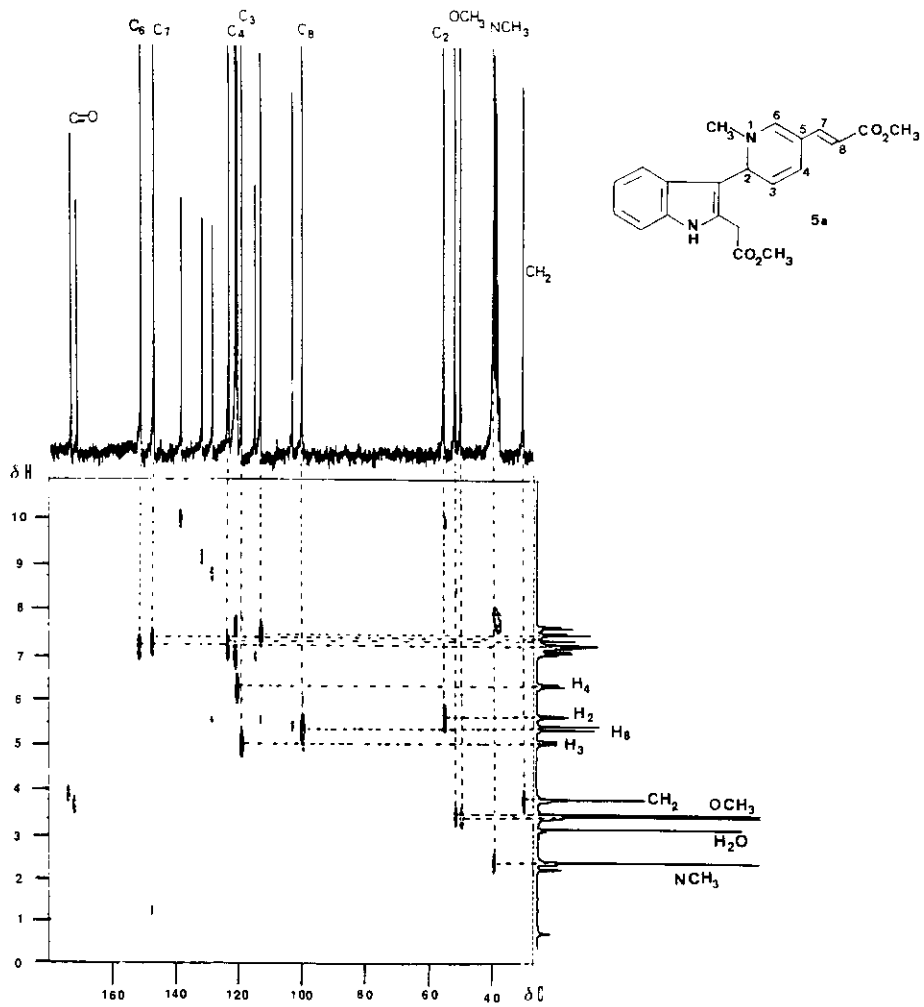


Figure 1. Two-dimensional nmr spectrum (HETCOR) of **5a** (d_6-DMSO)

The ^{1}H-^{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, 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}H- and ^{13}C-nmr data of 3-(dihydropyridyl)indoles **4** and **5** are showed in Table 1.

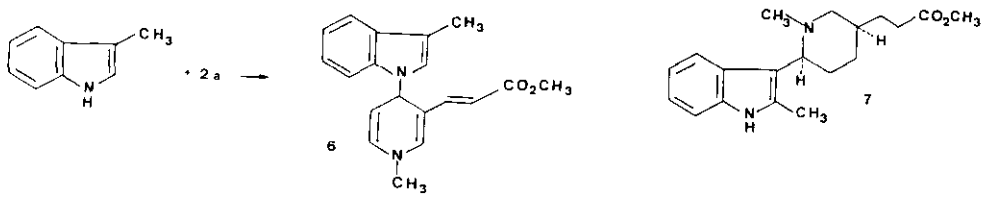
As could be expected, two requisites for the success of the reaction are the presence of an electron-withdrawing substituent at the 3-position of the pyridinium salt and the absence of substituent at the indole nitrogen. According with this, 2-methylindole (**1d**) failed to react with pyridinium salt **2e** under the usual reaction 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}H-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. ^{1}H- and ^{13}C-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)	----	4.79 dt (4.8, 1.2)	5.00 ddd (7.8, 4.8, 0.8)	5.94 ddd (7.8, 1.6, 1.2)	3.31 s	2.45 s	8.90 br s
	149.0	114.0	26.2	109.1	127.1	40.7	11.2	187.6
5a[e]	5.62 dd (3.6, 2.0)	5.09 dd (10.0, 3.6)	6.25 dt (10.0, 2.0)	----	7.09[f] d (2.0)	2.64 s	3.62[g] s, 3.92 s	3.57[g] s, 5.39 d, 7.15 d (16.0) (16.0)
	55.2	116.9	118.4	101.7	148.2	40.0	170, 51.8[g], 31.2	168.2, 144.2, 98.7, 50.0[g]
5b	5.46 dd (3.8, 1.2)	5.27 dd (10.0, 3.8)	6.29 dt (10.0, 1.2)	----	6.53 d (1.2)	2.77 s	----	3.73 s, 5.55 d, 7.25 d (15.0) (15.0)
	57.1	117.2	119.5	103.3	146.4	41.2	----	169.7, 144.3, 100.9, 50.8
5c	5.58 dd (3.8, 1.2)	5.18 dd (9.6, 3.8)	6.27 dt (9.6, 1.2)	----	6.57 d (1.2)	2.69 s	2.42 s	3.72 s, 5.53 d, 7.25 d (14.7) (14.7)
	54.7[e]	116.4	118.0	101.1	147.6	39.4	10.5	167.6, 143.6, 97.8, 49.5
5d	5.67 dd (3.5, 1.9)	5.20 dd (10.2, 3.5)	6.58 ddd (10.2, 1.9, 0.6)	----	7.38 d (0.6)	2.88 s	2.46 s	8.72 br s
	57.9[h]	116.0	118.9	108.6	155.6	41.0	11.3	182.3
5e	5.55 dd (3.6, 1.8)	5.01 dd (10.1, 3.6)	6.56 br d (10.1)	----	7.41 br s	2.77 s	2.42 s	2.20 s
	55.9	114.2	118.3	106.2	149.2	41.2	11.3	190.0, 23.8
6[e,i]	6.95 d (2.6)	----	6.11 d (4.4)	4.94 dd (7.8, 4.4)	6.40 br d (7.8)	3.27 s	2.17 s	3.47 s, 5.24 d, 7.28 d (15.4) (15.4)
	145.7	105.4	47.4	109.5	130.4	40.8	9.6	167.2, 141.5, 102.9, 50.6

[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 δ 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: $CH{=}CH{-}CO_2CH_3$



pyridine in which the γ-substituent is 3-methyl-1-indolyl rather than 3-methyl--3*H*-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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6. The general procedure was: i) 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.

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9. Minor amounts of 1,4-dihydropyridine **4b** were detected by ^{1}H-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 ß-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-methyltetrahydropyridine-3-acrylates.
16. For the synthesis of 3-(2-piperidyl)indoles, see: (a) J. C. Powers, J. Org. Chem., 1965, **30**, 2534; (b) E. Wenkert, K. G. Dave, and F. Haglid, J. Am. Chem. Soc. 1965, **87**, 5461; (c) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, J. Org. Chem., 1968, **33**, 747; (d) T. Kametani and T. Suzuki, J. Org. Chem., 1971, **36**, 1291; (e) M. Feliz, J. Bosch, D. Mauleón, M. Amat, and A. Domingo, J. Org. Chem., 1982, **47**, 2435 and references cited therein.
17. **7**: ^{1}H-nmr ($CDCl_3$, δ) 1.93 (s, 3 H, CH_3), 2.19 (dd, J=12, 3.2 Hz, 1 H, H-6ax), 2.33 (s, 3 H, NCH_3), 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, OCH_3), 6.99-7.21 (m, 3 H, ArH), 7.79-7.86 (m, 1 H, ArH), 7.96 (s, 1 H, NH). The picrate[10] melted at 158-160 °C (acetone-ether).

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