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NUCLEOPHILIC ADDITION OF 2-INDOLYLACYL ANION EQUIVALENTS TO N-ALKYLPYRIDINIUM SALTS

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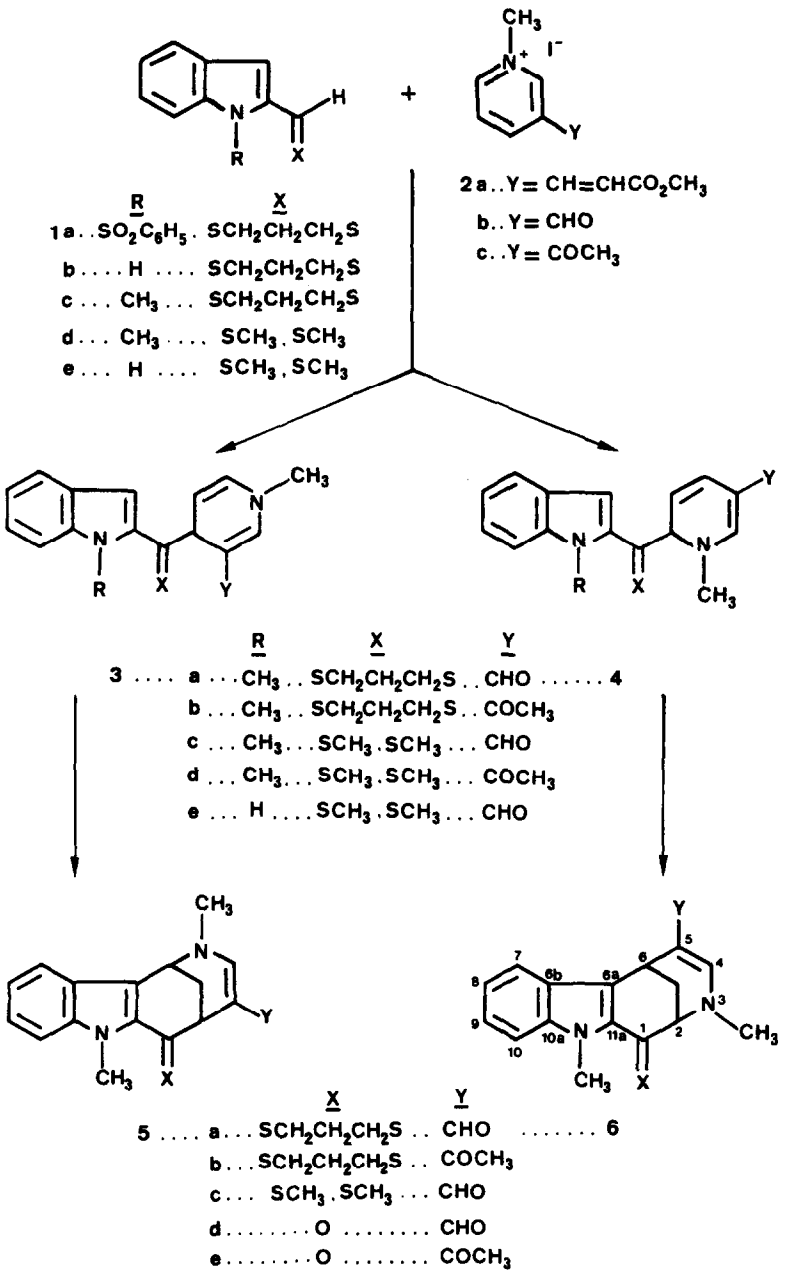
The reactions of the anions derived from dithianes **1a–c** and bis(methylthio)acetals **1d,e** with N-alkylpyridinium salts **2a–c** are reported.

The addition of stabilized carbon nucleophiles to N-alkylpyridinium salts has proved to be a useful method of forming carbon-carbon bonds to give substituted dihydropyridines, which can be further elaborated into complex polycyclic alkaloid systems.[1] In this context, we have recently reported[2] that the use of the lithium enolates of 1-, 2-, and 3-indoleacetic esters as nucleophiles in the above reaction allows, after acid cyclization of the resulting 1,4-dihydropyridines, the straightforward construction of suitably functionalized tetracyclic ABCD ring substructures of C-mavacurine, Strychnos, and akuammiline alkaloids, respectively.

We are interested in the extension of the above addition-cyclization sequence to 2-indolylacyl anion equivalents in order to evaluate if it could constitute a synthetic way of constructing the tetracyclic 6-oxo-1,5-methanoazocino[4,3-b]indole system present in some 2-acylindole alkaloids.[3] To our knowledge the addition of this kind of nucleophiles to pyridinium salts has not previously been studied. This Letter deals with our initial results in this field operating with the anions derived from (dithianyl)indoles **1a–c** and bis(methylthio)acetals **1d,e** as starting nucleophiles.

Our first experiments were not encouraging since, after addition of the anions derived from **1a**[4] and **1b**[4] to pyridinium salts **2a** or **2b** (THF, -30 °C, 1.5 h) and further acidic treatment (C_6H_6-HCl, -50 °C to rt, 3 h), the starting dithianes were recovered unchanged. However, the use of the same set of conditions from (dithianyl)indole **1c**[5] and pyridinium salts **2b** or **2c** afforded tetracycles **6a**[6] and **6b**[9] in 35% and 23% yields, respectively.[10] The expected Strychnos-type tetracyclic systems **5** were not detected. When the acidic treatment was omitted in the reaction with **2b**, the 1,2-dihydropyridine **4a**[11] (δC-2 69.3), which was further cyclized to **6a**, was isolated in 30% yield. These results imply that the addition has taken place at the α-position of the pyridinium salt and that the equilibration of the kinetic products (1,2-dihydropyridines **4a,b**) to the expected 1,4-dihydropyridines **3a,b** does not occur. The different behaviour of the dithiane anions here employed as compared with that of the enolates of methyl indole-2-acetates[2] can be explained by considering both the harder character, which induces only attack at the α-position, and the lower stability,



that disfavours the equilibration, of the former.

Taking into account that open-chain dithioacetals have a softer nucleophilic character than cyclic ones,[12] it could be expected that the use of bis(methylthio)acetals **1d,e**[13] increased the ability of the corresponding anions to attack at the γ-position of the pyri-

TABLE 1. Significant ^{13}C-NMR Data of Tetracycles 6[a]

	C-1	C-2	C-4	C-5	C-6	C-12	N-CH_3	X	Y
6a	54.1	62.4	154.1	117.8	20.8	25.0	32.9, 46.9	23.7, 28.9, 29.4	184.2
6b	54.4	61.2	147.6	115.4	21.4	25.1	32.9, 47.1	23.8, 29.0, 29.5	23.5, 190.9
6c	59.8	67.1	153.1	119.1	21.0	26.7	31.7, 46.2	14.1, 14.9	184.8
6d	182.5	64.0	150.0	115.0	21.6	28.9	31.3, 42.5	----	184.3
6e	183.1	62.7	143.8	112.7	21.9	28.6	31.1, 42.5	----	23.1, 190.9

[a] Chemical shifts in ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz.

TABLE 2. Significant ^{13}C-NMR Data of Dihydropyridines 3 and 4[a]

	C-2	C-3	C-4	C-5	C-6	N-CH_3	C=X	X	CHO
3c	149.3	109.2	38.9	105.2	130.7	31.8, 40.0	69.5	12.9, 14.0	187.9
4a	69.3	110.6	121.5	111.7	155.7	32.9, 45.3	63.9	24.2, 27.5, 28.2	184.5
4c	68.9	110.1	120.6	112.0	156.2	32.8, 44.6	69.5	13.1, 14.5	184.0
4e	67.8	110.9	121.6	111.5	155.5	45.2	69.2	12.3, 12.6	184.1

[a] Chemical shifts in ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz.

dinium ring. In fact, exposure of the anion derived from **1d** to salt **2b** under the usual conditions gave a 1:1 mixture of the unstable 1,4- and 1,2-dihydropyridines **3c**[14] (δC-4 38.9) and **4c**[15] (δC-2 68.9) in 15% yield, thus pointing out that the γ-attack had occurred to some extent. However, rather surprisingly, when the addition was followed by cyclization (C_6H_6-HCl, rt, 3 h), without isolating the intermediate dihydropyridines, a 1:5 mixture of the unnatural-type tetracycles **6c**[16] and **6d**[17] (formed by deprotection of **6c**) was obtained in 20% yield. In accordance with this result, all attempts to separately cyclize the isolated 1,4-dihydropyridine **3c**, even under milder conditions (AcOH), resulted in decomposition. A similar result was obtained when the addition-cyclization sequence was effected from dithioacetal **1d** and pyridinium salt **2c**:[10] tetracycle **6e**[18] was obtained in 16% yield.

In contrast, the dianion derived from the N-unsubstituted indole **1e** reacted with salt **2b** to give, although in low yield (7%), 1,2-dihydropyridine **4e**[19] (δC-2 67.8) as the only isolable product which decomposed during the cyclization attempts.

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6. **6a**:[7] m.p. 250-251 °C (acetone); ^{1}H-NMR[8] ($CDCl_3$) 1.60 (dm, 13 Hz, 1 H, 12-H), 2.05 (m, 3 H, CH_2CH_2S and 12-H), 2.80 (m, 4 H, CH_2S), 3.40 (s, 3 H, NCH_3), 3.91 (d, 4.1 Hz, 1 H, 2-H), 4.09 (s, 3 H, NCH_3), 4.30 (t, 2 Hz, 1 H, 6-H), 6.71 (s, 1 H, 4-H), 7.02-7.20 (m, 3 H, ind), 7.96 (d, 7.8 Hz, 1 H, 7-H), 8.83 (s, 1 H, CHO).
7. This compound gave satisfactory elemental analysis.
8. A positive NOE effect for the signals corresponding to 6-H and 2-H on irradiation of the signals due to 7-H and 3-CH_3, respectively, was observed.
9. **6b**:[7] m.p. 264-265 °C (acetone-MeOH); ^{1}H-NMR ($CDCl_3$) 1.65 (dm, 14 Hz, 1 H, 12-H), 2.09 (s, 3 H, CH_3CO), 2.15 (m, 3 H, CH_2CH_2S and 12-H), 3.01 (m, 4 H, CH_2S), 3.49 (s, 3 H, NCH_3), 3.94 (dt, 4 and 1.5 Hz, 1 H, 2-H), 4.12 (s, 3 H, NCH_3), 4.53 (t, 2.4 Hz, 1 H, 6-H), 7.05-7.20 (m, 4 H, ind and 4-H), 8.03 (dm, 8 Hz, 1 H, 7-H).
10. Operating from the less reactive pyridinium salt **2a** the starting dithioacetal was recovered.
11. **4a**: ^{1}H-NMR ($CDCl_3$) 1.89 (m, 2 H, CH_2CH_2S), 2.73 (m, 4 H, CH_2S), 2.89 (s, 3 H, NCH_3), 4.04 (s, 3 H, NCH_3), 4.82 (d, 5.2 Hz, 1 H, pyr 2-H), 5.19 (dd, 10 and 5.2 Hz, 1 H, pyr 3-H), 6.70 (d, 10 Hz, 1 H, pyr 4-H), 6.90 (br s, 1 H, pyr 6-H), 7.08 (s, 1 H, ind 3-H), 7.10-7.40 (m, 3 H, ind), 7.60 (d, 7.6 Hz, 1 H, ind 4-H), 8.85 (s, 1 H, CHO).
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13. Compounds **1d**[7] (82%) and **1e**[7] (81%) were prepared by thioacetalization of the corresponding aldehydes (excess CH_3SH, TsOH, CH_2Cl_2, -30 °C, 1 h). THF solutions of anions derived from **1d** and **1e** were available by treatment with 1.1 or 2.2 equivalents, respectively, of n-BuLi at -70 °C for 0.5 h.
14. **3c**: ^{1}H-NMR ($CDCl_3$) 2.00 and 2.07 (2 s, 3 H, SCH_3), 2.86 (s, 3 H, NCH_3), 4.17 (s, 3 H, NCH_3), 4.49 (d, 5.6 Hz, 1 H, pyr 4-H), 4.94 (dd, 7.5 and 5.6 Hz, 1 H, pyr 5-H), 5.90 (d, 7.5 Hz, 1 H, pyr 6-H), 6.75 (s, 1 H, ind 3-H), 6.78 (s, 1 H, pyr 2-H), 7.05-7.40 (m, 3 H, ind), 7.55 (m, 1 H, ind 4-H), 9.15 (s, 1 H, CHO).
15. **4c**: ^{1}H-NMR ($CDCl_3$) 1.91 and 2.15 (2 s, 3 H, SCH_3), 2.75 (s, 3 H, NCH_3), 4.14 (s, 3 H, NCH_3), 5.18 (d, 5 Hz, 1 H, pyr 2-H), 5.30 (dd, 9.5 and 5 Hz, 1 H, pyr 3-H), 5.65 (d, 9.5 Hz, 1 H, pyr 4-H), 6.93 (br s, 1 H, pyr 6-H), 6.94 (s, 1 H, ind 3-H), 7.02-7.65 (m, 4 H, ind), 8.85 (s, 1 H, CHO).
16. **6c**: ^{1}H-NMR ($CDCl_3$) 1.64 (dm, 12 Hz, 1 H, 12-H), 1.69 (s, 3 H, SCH_3), 2.31 (s, 3 H, SCH_3), 2.70 (dt, 12 and 2.9 Hz, 1 H, 12-H), 3.54 (s, 3 H, NCH_3), 3.90 (m, 1 H, 2-H), 4.06 (s, 3 H, NCH_3), 4.35 (t, 2.9 Hz, 1 H, 6-H), 6.74 (s, 1 H, 4-H), 7.08-7.25 (m, 3 H, ind), 8.03 (d, 7.6 Hz, 1 H, 7-H), 8.90 (s, 1 H, CHO).
17. **6d**:[7] m.p. 246-247 °C (acetone); ^{1}H-NMR[8] ($CDCl_3$) 1.86 (dt, 12.7 and 3.3 Hz, 1 H, 12-H), 2.39 (dt, 12.7 and 2.8 Hz, 1 H, 12-H), 3.21 (s, 3 H, NCH_3), 3.84 (m, 1 H, 2-H), 4.01 (s, 3 H, NCH_3), 4.49 (t, 2.8 Hz, 1 H, 6-H), 6.68 (s, 1 H, 4-H), 7.10-7.40 (m, 3 H, ind), 8.19 (d, 8.1 Hz, 1 H, 7-H), 8.80 (s, 1 H, CHO).
18. **6e**:[7] m.p. 228-229 °C (acetone); ^{1}H-NMR ($CDCl_3$) 1.85 (dt, 12.5 and 4 Hz, 1 H, 12-H), 2.08 (s, 3 H, CH_3CO), 2.39 (dt, 12.5 and 2.5 Hz, 1 H, 12-H), 3.21 (s, 3 H, NCH_3), 3.78 (m, 1 H, 2-H), 4.03 (s, 3 H, NCH_3), 4.63 (t, 2.5 Hz, 1 H, 6-H), 7.10-7.40 (m, 4 H, ind and 4-H), 8.25 (d, 8.1 Hz, 1 H, 7-H).
19. **4e**: ^{1}H-NMR ($CDCl_3$) 2.04 and 2.09 (2 s, 3 H, SCH_3), 3.17 (s, 3 H, NCH_3), 4.71 (dd, 5.5 and 1 Hz, 1 H, pyr 2-H), 5.39 (dd, 9.6 and 5.5 Hz, 1 H, pyr 3-H), 6.59 (br s, 1 H, pyr 6-H), 6.62 (s, 1 H, ind 3-H), 6.67 (br d, 9.6 Hz, 1 H, pyr 4-H), 7.01-7.20 (m, 2 H, ind), 7.29 (dd, 8 and 1 Hz, 1 H, ind 7-H), 7.50 (dd, 7.5 and 1 Hz, 1 H, ind 4-H), 8.40 (s, 1 H, CHO), 8.90 (br s, 1 H, NH).

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