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NUCLEOPHILIC ADDITION OF INDOLE-2-ACETIC ESTER ENOLATES TO *N*-ALKYLPYRIDINIUM SALTS. A FORMAL SYNTHESIS OF THE *STRYCHNOS* ALKALOIDS TUBIFOLIDINE AND TUBIFOLINE

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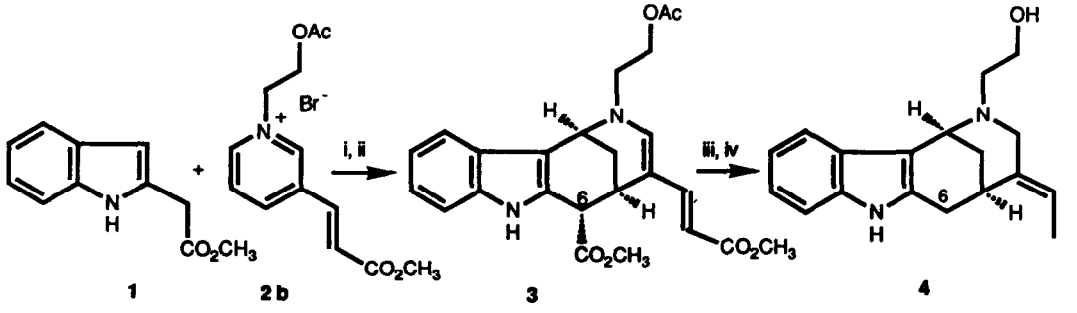
Abstract: An efficient route for the synthesis of tetracyclic ABCD ring substructures of *Strychnos* alkaloids that incorporate the C-16 oxidized one-carbon substituent characteristic of the curan series and a formal synthesis of the nor-curan type alkaloids tubifolidine and tubifoline is reported.

In a previous work we have reported[1] the synthesis of the tetracyclic alcohol **4** by nucleophilic addition of the enolate of ester **1** to pyridinium salt **2b**, followed by acid cyclization of the resulting 1,4-dihydropyridine and further elaboration of the ethylidene substituent (Scheme 1). Decarbomethoxylation at C-6 occurred during the latter transformation. Alcohol **4** can be considered a potential precursor of the pentacyclic *Strychnos* alkaloids[2] of the nor-curan type tubifoline and tubifolidine as we have recently developed a new synthetic entry to these alkaloids based on the closure of the five-membered E ring in the last synthetic steps from an appropriately *N*-substituted hexahydro-1,5-methanoazocino[4,3-*b*]indole system that incorporates rings ABCD of *Strychnos* alkaloids[3]. However most of pentacyclic *Strychnos* alkaloids possess an oxidized one-carbon substituent at C-16 (corresponding to C-6 in tetracycle **4**). Although the C-16 methoxycarbonyl group could be reintroduced in a subsequent synthetic step, thus allowing the synthesis of 19,20-dihydroakuammicine (curan type)[3, 4], from a synthetic standpoint the above decarboxylation did represent an inconvenience to overcome.

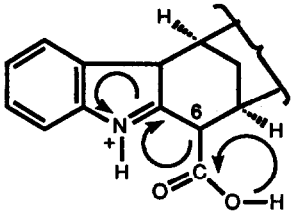


Reagents and Conditions. i: LDA, THF, 1.5 h, -78° C to -30°C; ii: Benzene-HCl, 1.5 h, -20°C (pH=3-4); iii: 4N HCl, 4h, 100°C; iv: $NaBH_4$, MeOH, 0°C, 1h.

SCHEME 1

In this Letter we report a) the preparation of the C-6 methoxycarbonyl substituted tetracycles **7** by a related procedure that implies the use of the enolate of the *N*-protected indole-2-acetate **5** as the starting nucleophile (Scheme 2) and b) a formal total synthesis of (±)-tubifoline and (±)-tubifolidine taking advantage of the tetracyclic alcohol **4** (Scheme 3).

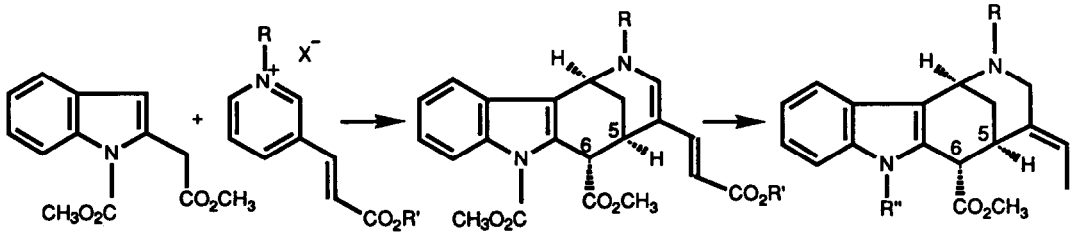
The observed loss of the C-6 methoxycarbonyl group of **3** takes place during the hydrolytic step required for the hydrolysis and decarboxylation of the β-(tetrahydro-3-pyridyl)acrylate moiety, by way of an intermediate **A** in which the indole 3-position has undergone protonation. We felt that protecting the indole nitrogen with an electron withdrawing substituent such as methoxycarbonyl would inhibit the protonation and, consequently, would allow the chemoselective decarboxylation of the doubly vinylogous urethane moiety without affecting the C-6 carboxy group.



A

Condensation of the enolate derived from ester **5**[5] with pyridinium salts **2a**[7] and **2b**[8] followed by treatment with dry HCl in benzene afforded tetracycles **6a**[9] and **6b**[10], respectively, in approximately 30% overall yield[11]. As expected, treatment of **6a,b** with refluxing 4N aqueous HCl followed by reesterification with methanolic HCl and further reduction with $NaBH_4$ gave the C-6 substituted ethylidene-bearing tetracycles **7a**[12] and **7b**[13] in 40 and 30% yields, respectively. Similar results were obtained when using pyridinium salt **2c**[6] which incorporates a *tert*-butyl acrylate moiety: the cyclized product **6c**[11,14] (23% yield) and then the ethylidene derivative **7b** (32% yield) were obtained.

It is worth mentioning that the elaboration of the ethylidene substituent from the *tert*-butyl vinylogous urethane **6c** was also accomplished under non-hydrolytic conditions, by heating **6c** with methanolic HCl followed by $NaBH_4$ reduction. In this manner, the indole-protected tetracycle **7c**[15], which could be further converted (90% yield) to **7b** by alkaline hydrolysis (10%KOH/MeOH-H_2O) followed by reesterification of the C-6 carboxy group, was obtained. The most significant ^{13}C-NMR chemical shifts of tetracycles **6** and **7** are given in Table 1.



5 **2**... a...R=CH_3; R'=CH_3 ..... **6**
b...R=CH_2CH_2OAc; R'=CH_3
c...R=CH_2CH_2OAc; R'=*t*-Bu

7 ....a...R=CH_3; R"=H
b...R=CH_2CH_2OH; R"=H
c...R=CH_2CH_2OH; R"=CO_2CH_3

SCHEME 2

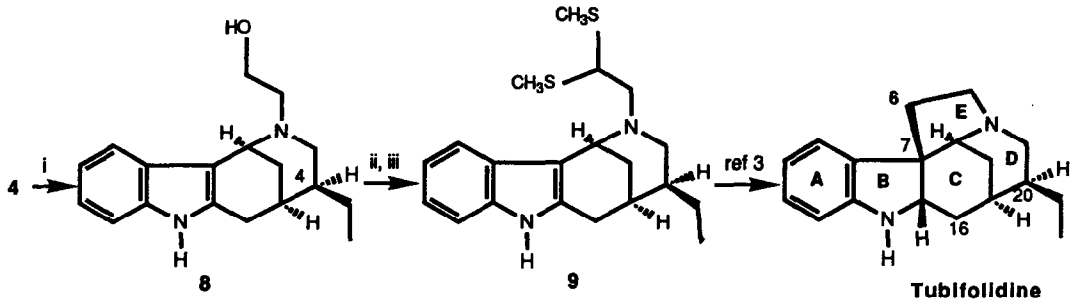
Tetracycles **4** and **7b** possess four of the five rings of the *Strychnos* alkaloids and incorporate both their characteristic two-carbon substituent at the piperidine β-position and a hydroxyethyl chain at the piperidine nitrogen which can allow further closure of E ring by formation of the C-6/C-7 bond.

Table 1. Significant ^{13}C-NMR Chemical Shifts[a] of Tetracycles 6, 7, and 8

	C-1	C-3	C-4	C-5	C-6	C-12	CO	OCH_3	CH_2CH_3, CH=CH or $=CHCH_3$
6a	48.4	146.0	108.1	29.8	46.9	24.4	151.9, 169.5, 172.5	50.7, 52.1, 53.5	103.0, 144.3
6b	47.5	145.6	108.7	30.2	46.8	24.9	151.9, 169.2, 170.6, 172.2	50.9, 53.3, 53.7	104.2, 142.7
6c	47.5	144.3	108.8	30.2	46.8	24.9	151.9, 168.2, 171.0, 172.2	52.3, 53.7	106.9, 142.0
7a	51.7	56.0	134.7	31.1	45.5	34.4	172.2	51.8	12.5, 119.2
7b	51.5	57.8	136.6	31.1	45.3	31.3	172.0	53.3	13.2, 120.5
8	50.9	49.8	28.4	41.2	24.3	33.8	-	-	11.4, 22.3

a: In ppm relative to TMS. Measured in $CDCl_3$ solution. 50 Mz.

This proposition was experimentally confirmed by converting alcohol **4** to dithioacetal **9**, which had previously been prepared by an alternative way and converted to the *Strychnos* alkaloids of the nor-curan type tubifolidine[3, 16] and tubifoline[3, 17]. Thus, catalytic hydrogenation of **4** took place stereoselectively to give **8**[18], having the same relative configuration at C-4 as the alkaloids at the corresponding position C-20. Oxidation of **8** with DMSO-TFAA followed by trapping of the resultant unstable aldehyde with excess methanethiol afforded dithioacetal **9** in 36% yield.



Reagents and Conditions. i: PtO_2/H_2, MeOH; ii: DMSO-TFAA, CH_2Cl_2, -60°C-30 min, rt-40 min; iii: $BF_3.Et_2O$-CH_3SH, Benzene, -10°C.

SCHEME 3

ACKNOWLEDGEMENT. This work was supported by the DGICYT, Spain (project PB88-0316).

REFERENCES AND NOTES

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2. For a review about pentacyclic *Strychnos* indole alkaloids, see: J. Bosch and J. Bonjoch in "Studies in Natural Product Chemistry" vol 1, Atta-ur-Rahman ed., Elsevier, Amsterdam, p. 31, **1988**.
3. M. Amat, A. Linares, and J. Bosch, *J. Org. Chem.*, submitted.

4. M. Amat, A. Linares, and J. Bosch, *Tetrahedron Lett.*, **1989**, *30*, 2293.
5. The synthesis of 5[6] was accomplished as follows: starting with 2-methylindole, the dilithium salt of 1-hydroxycarbonyl-2-indoleacetic acid was obtained (see: A.R. Katritzky and K. Akutagawa, *J. Am. Chem. Soc.*, **1986**, *108*, 6808). Acidification of the salt with cold 2N H_2SO_4 and treatment of the resulting diacid with excess diazomethane afforded **5** in 67% overall yield.
6. This compound gave elemental analysis consistent with the proposed structure.
7. a) C. Besselièvre, R. Beugelmans, and H.-P. Husson, *Tetrahedron Lett.*, **1976**, 3447.
   b) M. Alvarez, R. Lavilla, and J. Bosch, *Tetrahedron Lett.*, **1987**, *28*, 4457.
8. J. Bosch, M.-L. Bennasar, E. Zulaica ,and M. Feliz, *Tetrahedron Lett.*, **1984**, *25*, 3119.
9. **6a**[6]: ^{1}H-NMR ($CDCl_3$, δ) 1.89 (ddd, J= 12.6, 2.4, 2.2 Hz, 1H, H-12), 2.2 (dt, J= 12.6, 1.6 Hz, 1H, H-12), 3.11 (s, 3H, NCH_3), 3.18 (br s, 1H, H-5), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.33 (d, J=1.4Hz, 1H, H-6), 4.47 (t, 1H, H-1), 5.71 (d, J=15.2 Hz, 1H, H_{α} acrylate), 6.33 (s, 1H, H-3), 7.00-7.70 (m, 4H, ArH, H_{β} acrylate), 8.10 (m, 1H, H-8).
10. **6b** [6]: ^{1}H-NMR ($CDCl_3$, δ) 1.83 (ddd, J=12.5, 3.3, 3.1 Hz, 1H, H-12), 2.08 (s, 3H, CH_3CO), 2.23 (dt, J=12.5, 2.2 Hz, 1H, H-12), 3.20 (br s,1H, H-5), 3.36 (m, 1H, NCH_2), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.16 (m, 1H, OCH_2), 4.33 (d, J= 1.4 Hz, 1H, H-6), 4.44 (m, 1H, OCH_2), 4.65 (t, 1H, H-1), 5.74 (d, J=16.6Hz, 1H, H_{α} acrylate), 6.38 (s, 1H, H-3), 7.0-7.6 (m, 4H, ArH, H_{β} acrylate), 8.10 (m, 1H, H-8).
11. Trace amounts of the C-5/C-6 cis isomer were detected by ^{1}H-NMR.
12. **7a**[6]: ^{1}H-NMR ($CDCl_3$, δ) (C_6 epimeric mixture) 1.67, 1.73 (2 dd, 3H, CH_3C=), 2.29, 2.32 (2s, 3H, NCH_3), 2.0 (dt, 1H, H-12), 2.6-3.0 (m, 2H, H-3),3.73, 3.78 (2s, 3H, NCH_3), 4.22 (d, J=5.7 Hz, 1H, H-6), 4.26, 4.34 (2 t, 1H, H-1), 5.40, 5.52 (2q, 1H, CH=), 7.1-7.7 (m, 4H, ArH), 8.5 (br s, 1H, NH).
13. **7b** : ^{1}H-NMR ($CDCl_3$, δ) 1.65 (dd, 3H, CH_3C=), 2.04 (br s, 1H, H-12), 2.34 (dt, 1H, H-12), 2.61-3.19 (m, 5H, 2H-3, NCH_2, OH), 3.54-3.77 (m, 4H, OCH_2, H-5, H-6), 3.70, (s, 3H, CH_3O), 4.19 (t, 1H, H-1), 5.27 (q, 1H, CH=), 7.01-7.54 (m, 4H, ArH), 8.43 (br s, 1H, NH).
14. **6c** [6]: ^{1}H-NMR ($CDCl_3$, δ) 1.51(s, 9H, *t*-Bu), 1.80 (dm, 1H, H-12), 2.08 (s, 3H, CH_3CO), 2.20 (dt, 1H, H-12), 3.20 (br s, 1H, H-5), 3.36 (m, 1H, NCH), 3.77 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.17 (m, 1H, CH_2O), 4.34 (d, J= 1.2 Hz, 1H, H-6), 4.40 (m, 1H, CH_2O), 4.62 (t, 1H, H-1), 5.69 (d, J =16 Hz, 1H, H_{α} acrylate), 6.34 (s, 1H, H-3), 7.09-7.60 (m, 4H, ArH, H_{β} acrylate), 8.09 (m, 1H, H-8).
15. **7c** : ^{1}H-NMR ($CDCl_3$, δ) 1.76 (dd, 3H, CH_3C=), 2.05 (t, 1H, H-12), 2.35 (dt, 1H, H-12), 2.7-3.1 (m, 5H, 2H-3, NCH_2, OH), 3.49 (br s, 1H, H-5), 3.6 (m, 2H, CH_2O), 3.74 (s, 3H, CH_3O), 4.00 (s, 3H, CH_3O), 4.04 (d, J=1.2 Hz, 1H, H-6), 4.21 (t, 1H, H-1), 5.37 (q, 1H, CH=), 7.1-7.6 (m, 3H, ArH), 8.15 (dd, 1H, H-8).
16. M. Amat, A. Linares, M.-L. Salas, M. Alvarez, and J. Bosch, *J. Chem. Soc. ,Chem. Commun.*, **1988**, *420*.
17. M. Amat, A. Linares, J. Muñoz, and J. Bosch, *Tetrahedron Lett.*, **1988**, *29*, 6373.
18. **8**[6]: ^{1}H-NMR ($CDCl_3$, δ) 0.94 (t, 3H, CH_3), 1.25 (m, 2H, CH_2), 1.85-1.95(m, 2H, H-3, H-5), 1.97 (dt, 1H, H-12), 2.2-2.45 (m, 3H, H-12, H-4, NCH_2), 2.67 (d, 1H, H-3), 2.80 (d, 1H, H_6), 3.1 (m, 1H, NCH_2), 3.4-3.85 (m, 4H, CH_2OH, H-6), 4.35 (t, 1H, H-1), 6.95-7.35 (m, 3H, ArH), 7.15 (dd, 1H, H-8), 8.36 (br s, 1H, NH).

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