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STUDIES ON THE SYNTHESIS OF *STRYCHNOS* INDOLE ALKALOIDS. A DIRECT ENTRY TO 4-ETHYLIDENE-HEXAHYDRO-1,5-METHANOAZOCINO[4,3-*b*]INDOLES

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A short, new route to the title tetracyclic substructure of *Strychnos* alkaloids, consisting in the nucleophilic attack of an ester α-anion to a pyridinium salt, acid-induced cyclization of the resultant 1,4-dihydropyridine, and stereospecific elaboration of the ethylidene substituent, is reported.

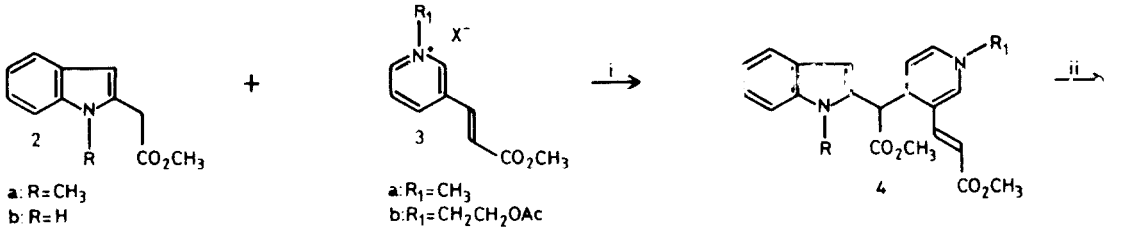
The hexahydro-1,5-methanoazocino[4,3-*b*]indole system constitutes the tetracyclic framework of indole alkaloids uleine and dasycarpidone. This ring system possesses four of the five rings of pentacyclic *Strychnos* indole alkaloids. These alkaloids are characterized by an additional two-carbon chain connecting the piperidine nitrogen and the indole 3-position (E ring), an ethyl or ethylidene substituent at the 20-position, and, usually, a functionalized one-carbon substituent at the 16-position (biogenetic numbering[1]).

We have recently reported a new synthetic entry to the pentacyclic ring skeleton of *Strychnos* indole alkaloids based on the closure of the five membered E ring in the last steps of the synthesis by cyclization upon the indole 3-position of an appropriately *N*-substituted 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system.[2]

We present here a short, efficient synthetic route to the above mentioned tetracyclic system. This route allows to incorporate the characteristic C-16[3] and C-20 appendages present in the *Strychnos* alkaloids (corresponding to the C-6 and C-4 positions, respectively, in the systematic numbering of **1**). The synthesis involves intermolecular addition of an appropriate carbon nucleophile upon the γ-position of a pyridinium salt having an electron-withdrawing substituent at the β-position, regiospecific acid promoted cyclization of the resulting 1,4-dihydropyridine,[4] and stereospecific elaboration of the ε-ethylidene group.[5] We employed a similar three-step reaction sequence in the first total synthesis of the bridged indole alkaloid vinoxine.[6]

Exposure of pyridinium salts **3a**[7,8] and **3b**[6] to the lithium enolate of ester **2a**[7,9] and then to acid afforded tetracycles **5a**[7,10] and **5b**,[7,11] respectively, in both cases accompanied by the corresponding C-6 epimers as minor components (3:1 ratio; overall yields 60-70%). When the above two-step sequence was effected from ester **2b**[12] and pyridinium salt **3a**, a mixture of the anticipated cyclized product **5c**[7,13] (50%; only trace amounts of the 5-H/6-H *cis*-isomer) and the unexpected regioisomer **7** (<5%),[14] in which cyclization had occurred upon the indole nitrogen, was obtained.[15]

The straightforward construction of the bridged system **5** further illustrates

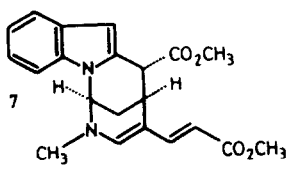


a: R=CH_3; R_1=CH_3
b: R=CH_3; R_1=CH_2CH_2OAc
c: R=H; R_1=CH_3

	R	R_1	R_2
a	CH_3	CH_3	CO_2CH_3
b	CH_3	CH_2CH_2OH	CO_2CH_3
c	H	CH_3	CO_2CH_3
d	H	CH_3	H

REAGENTS: i: LDA, THF, 2h, -78ºC → 30ºC; ii: C_6H_6-HCl, 2h, -30ºC (pH 3-4); iii: 4 N HCl, 1-2h, 100ºC; iv: a) 1.2 N MeOH-HCl, 16h, r.t. b) $NaBH_4$, MeOH, 1h, 0ºC.

that the scope of the general scheme of alkaloid synthesis developed by Wenkert[4] can be extended to the synthesis of bridged polycyclic systems fused to the indole nucleus.[16]



Tetracycles **5a-c** (C-6 epimeric mixtures were used) were elaborated in 30-40% yield into *E*-ethylidene derivatives **1** by treatment with refluxing aqueous 4N HCl, followed by reesterification of the C-6 carboxy group in the intermediate **6** and subsequent sodium borohydride reduction of the conjugated iminium salt.[17] In the two first cases (series *a* and *b*) this three-step sequence afforded C-6 epimeric mixtures, from which the 5-H/6-H *cis*-isomers could be separated and characterized.[18,19] In the *N*-unsubstituted indole series decarboxylation of the C-6 carboxy group occurred during the hydrolytic step, and a mixture of the expected ester **1c** and the C-6 unsubstituted tetracycle **1d**[7,20] (major component) was formed.

The assignment of the relative configuration at C-6 in tetracycles **5** (and their C-6 epimers), **7**, and **1** was done by ^{1}H-NMR from the coupling constant value of the doublet due to 6-H (J=1.5 Hz for a 5-H/6-H *trans*-relationship and J=5.5-7 Hz for a *cis*-relationship).[21] The most significant ^{13}C-NMR chemical shifts of tetracycles **1** and **5** are given in Table 1. The shielding of C-12 by a γ-effect induced by the methoxycarbonyl group in the *trans*-isomers was also of stereochemical diagnostic value.

The *N*-hydroxyethyl substituent of **1b** can allow further elaboration of ring E of *Strychnos* indole alkaloids.

Table 1. Significant ^{13}NMR Chemical Shifts of Tetracycles 1 and 5*

	C-1	C-3	C-4	C-5	C-6	C-12	COO	OCH_3	-CH=CH- or -CH-CH_3
5a	49.1	146.2	107.3	30.3	44.0	25.9	171.8, 169.2	50.8, 52.5	145.1, 101.8
	#48.6	148.0	105.1	28.7	48.2	29.2	172.4, 169.4	50.9, 52.5	145.9, 101.9
5b$^{\phi}$	46.8	146.3	106.3	30.0	43.2	25.6	171.4, 167.9	50.3, 52.4	145.2, 100.4
	#47.0	147.9	105.6	28.9	47.9	29.3	172.3, 169.2	50.7, 52.3	144.9, 102.7
5c$^{\phi}$	48.0	146.0	106.3	29.2	44.1	25.6	171.3, 167.8	50.0, 51.2	145.9, 99.7
1b^{æ}	51.2	57.1	134.2	31.9	45.3	33.8	172.2	51.9	121.6, 12.6
1d	51.9	56.0	135.9	27.4	29.3	33.4	---	---	121.1, 12.4

* In ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. #Chemical shift values of the corresponding minor *cis*-H-5/H-6 epimers. $^{\phi}$In DMSO solution. æ H-5/H-6 *cis*-epimer.

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2. J. Bosch and M. Amat, *Tetrahedron Lett.*, **1985**, *26*, 4951.
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6. J. Bosch, M.-L. Bennasar, E. Zulaica, and M. Feliz, *Tetrahedron Lett.*, **1984**, *25*, 3119.
7. This compound gave elemental analysis consistent with the proposed structure.
8. C. Besselièvre, R. Beugelmans, and H.-P. Husson, *Tetrahedron Lett .*, **1976**, 3447.
9. Prepared by reaction of 2-lithio-1-methylindole with diethyl oxalate, followed by Wolff-Kishner reduction of the resultant keto ester[7] and esterification with diazomethane (overall yield 60%).
10. **5a**: m.p. 188-190ºC (acetone); ^{1}H-NMR ($CDCl_3$,δ) 1.98 and 2.28 (2dt, H-12), 3.14 (s, $N-CH_3$), 3.32 (br, H-5), 3.57 (s, $N-CH_3$), 3.76 (s, OCH_3), 3.82 (s, OCH_3), 3.98 (d, J= 1.5 Hz, H-6) 4.55 (t,H-1), 5.65 (d, J=15 Hz, =CH), 6.34(s, H-3), 7.09-7.39 (m, 4H, =CH, ArH), 7.61 (dd, H-8).
11. **5b**: m.p. 170-172ºC (acetone-ether); ^{1}H-NMR ($CDCl_3$,δ) 1.88 and 2.26 (2dt, H-12), 2.09 (s, $COCH_3$), 3.32 (m, 2H, H-5,NCH_2), 3.55 (s, NCH_3), 3.74 (s, OCH_3), 3.79 (s, OCH_3), 3.95 (d, J=1.5 Hz, H-6), 4.18 and 4.40 (2m, OCH_2), 4.52 (t, H-1), 5.65 (d, J=15 Hz, =CH), 6.34 (s,

H-3), 7.08-7.36 (m, 4H, =CH, ArH),7.56 (dd, H-8).

12. a) I. Hasan, E. R. Marinelli, L.-C. C. Lin, F. W. Fowler, and A. B. Levy, *J. Org. Chem.*, **1981**, *46*, 157. The use of diethyl oxalate, instead of dimethyl oxalate, in the reaction with 1-benzenesulfonyl-2-lithioindole allows easier manipulation (70% yield). b) D. D. Weller and D. W. Ford, *Tetrahedron Lett.*, **1984**, *25*, 2105. We acknowledge Professor Weller for providing us experimental details about the preparation of indole 2-acetic acid.

13. **5c**: m.p. 272-274ºC (acetone-ether); ^{1}H-NMR (DMSO,δ) 1.84 and 2.16 (2dt, H-12), 3.12 (s, N-CH_3), 3.60 (s, OCH_3), 3.72 (s, OCH_3), 3.78 (d, J=1.2 Hz, H-6), 4.67 (t, H-1), 5.37 (d, J=15 Hz, =CH), 6.73 (s, H-3), 6.93-7.34 (m, 4H, =CH, ArH), 7.63 (dd, H-8), 11.00 (s, NH).

14. **7**: ^{1}H-NMR ($CDCl_3$,δ) 2.09 and 2.72 (2dt, H-12), 3.09 (s, N-CH_3), 3.24 (br, H-5), 3.73 (s, OCH_3), 3.75 (s, OCH_3), 4.13 (d, J=1 Hz, H-6), 5.60 (d, J=15 Hz, =CH), 5.65 (t, H-1), 6.29 (s, H-3), 6.43 (s, H-7), 7.04-7.54 (m, 5H, =CH, ArH).

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16. See also: a) M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Tetrahedron*, **1983**, *39*, 3673; b) reference 6.

17. For the use of this procedure in the synthesis of *E*-ethylidene bearing indole alkaloids, see: a) R. Besselièvre, J.-P. Cosson, B. C. Das, and H.-P. Husson, *Tetrahedron Lett*, **1980**, *21*, 63; b) E. Wenkert, E. C. Angell, J. Drexler, P. D. R. Moeller, J. S. PyreK, Y.-J. Shi, M. Sultana, and Y. D. Vankar, *J. Org. Chem.*, **1986**, *51*, 2995; c) references 4c and 6.

18. The picrate[7] of **1a** melted at 207-210ºC (methanol): IR (KBr, cm^{-1}) 1730; ^{1}H-NMR (DMSO,δ) 1.67 (dd, J=6.9, 1.5 Hz, CCH_3), 2.08 and 2.24 (2dt, H-12), 3.31 (s, N-CH_3), 3.56 (s, N-CH_3) 3.65 (s, OCH_3), 4.65 (d, J=6.8 Hz, H-6), 5.03 (t, H-1), 5.68 (qd, =CH), 7.10-7.30 (m, 2H, ArH), 7.52 (d, 1H, ArH), 7.61 (d, 1H, ArH).

19. **1b**: The picrate[7] melted at 95-98ºC (methanol); IR ($CHCl_3$, cm^{-1}) 1730; ^{1}H-NMR ($CDCl_3$,δ), 1.67 (dd, J=6.8, 1.6 Hz, CCH_3), 1.92 (dt, 1H, H-12), 2.16-2.42 (m, 2H, NCH_2, H-12), 2.86-3.10 (m, 3H, NCH_2, H-3), 3.57 (s, N-CH_3), 3.69 (s, OCH_3), 4.20 (d, J=6.5 Hz, H-6), 4.34 (t, H-1), 5.46 (qd, =CH), 7.04-7.38 (m, 3H, ArH), 7.52 (d, H-8).

20. **1d**: m.p. 187-190ºC (acetone); ^{1}H-NMR ($CDCl_3$,δ) 1.67 (dd, J=6.8, 1.8 Hz, CCH_3), 1.94 and 2.18 (2dt, H-12), 2.33 (s, NCH_3), 2.59 (d, J=17 Hz, 1H, H_β-6), 2.72 (br d, J=13.2 Hz, H_a-3), 2.88 (d, J=13.2 Hz, H_e-3), 3.12 (dd, J=17, 6.6 Hz, H_α-6), 3.30 (br, H-5), 4.23 (t, H-1), 5.32 (qd, =CH), 7.10 (m, 2H, ArH), 7.30 (m, 1H, ArH), 7.54 (dd, 1H, ArH), 8.00 (br, NH).

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