Tetrahedron Letters,Vol.26,No.40,pp 4951-4954,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

A NEW SYNTHETIC ENTRY TO PENTACYCLIC *STRYCHNOS* INDOLE ALKALOIDS

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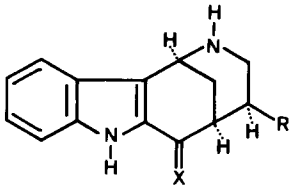
Cyclization of the thionium ion generated by DMTSF treatment of dithioacetal 15 constitutes a new synthetic entry to the pentacyclic ring system of *Strychnos* indole alkaloids.

Pentacyclic *Strychnos* indole alkaloids constitute one of the groups of indole alkaloids that has received less attention from a synthetic standpoint. Until the pioneering work of Van Tamelen,[1] all previously reported synthesis for these alkaloids converge to tetracyclic structures having the ring skeleton of stemmadenine, which are further subjected to transanular cyclization.[2] This methodology implies the simultaneous formation of C and E rings by electrophilic attack of an iminium salt on the indole 3-position.

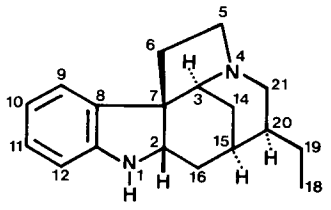
We describe here a new synthetic entry to pentacyclic *Strychnos* indole alkaloids based on the closure of the five membered E ring in the last synthetic steps from a tetracyclic 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole system. This proposition implies the integration of a functionalized two-carbon appendage on the piperidine nitrogen atom followed by intramolecular alkylation on the indole 3-position. A similar synthetic approach has been developed for the synthesis of some *Aspidosperma* alkaloids.[3,4]

As we recently reported,[5] photocyclization of 2-chloroacetyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indoles failed as a method for the elaboration of the E ring of *Strychnos* type systems because the cyclization occurred on the indole 4-position instead of the 3-position. Since cyclizations of 2-(phenylsulfinyl)acetyl derivatives of octahydropyrido[3,2-c]carbazoles on the indole 3-position under Pummerer conditions have been successfully used in the synthesis of *Aspidosperma* alkaloids,[4] we planned to apply a similar methodology to reach our purpose.

Although in a previous paper we reported the preparation of *N*-demethylisodasycarpidone (1),[6] which can be considered as a synthetic precursor of the pentacyclic *Strychnos* indole alkaloids tubifoline and tubifolidine, in order to evaluate the effectiveness of our proposal we selected as starting material for previous studies the simplified analogue 2,[7] lacking the C-20 two carbon substituent present in the greater part of indole alkaloids.



1: R=Et; X=O
2: R=H ; X=H,H



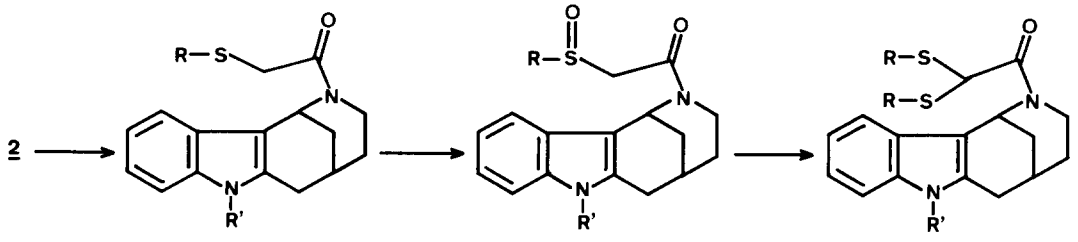
TUBIFOLIDINE

The required (phenylsulfinyl)acetamide 7[8] was prepared in three steps by acylation of 2 with (phenylthio)acetyl chloride (CH_2Cl_2, 1N NaOH) followed by tosylation of the indole nitrogen (*p*-TsCl, C_6H_6/50% NaOH, $Bu_4N.HSO_4$) and oxidation of the resulting sulfide 4 (*m*-CPBA, CH_2Cl_2, $NaHCO_3$).

Treatment of the sulfoxide 7 with TFAA (1.3 eq, 0°C, CH_2Cl_2, 10 min) followed by heating of the intermediate α-trifluoroacetoxysulfide[9] (135°C, chlorobenzene, 3 h) afforded the dithioacetal 10.[10] No cyclization products on the indole 3-position were detected.

In order to verify if the failure in the cyclization step could be attributed either to the deactivation of the protecting tosyl group or to the steric interactions due to the bulky phenyl substituent, the Pummerer rearrangement from the (phenylsulfinyl)acetamide 8 and from the (methylsulfinyl)acetamide 9 was investigated.

Sulfoxide 8 was prepared[8] by *m*-CPBA oxidation of sulfide 3 whereas (methylsulfinyl)acetamide 9 was obtained[8] similarly as described for 7. In both cases, treatment with TFAA (1:1 ratio of TFAA and Et_3N[11] at r.t. or at 80°C for compound 8; from 0°C to 135°C for compound 9) afforded again the corresponding dithioacetals, 11 and 12 respectively.



3: R=C_6H_5; R'=H
4: R=C_6H_5; R'=Ts
5: R=CH_3 ; R'=H
6: R=CH_3 ; R'=Ts

7: R=C_6H_5; R'=Ts
8: R=C_6H_5; R'=H
9: R=CH_3 ; R'=Ts

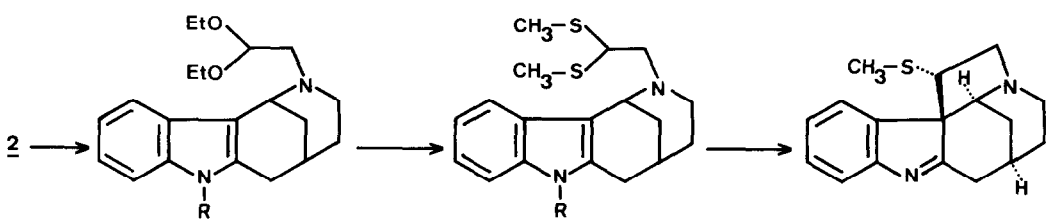
10: R=C_6H_5; R'=Ts
11: R=C_6H_5; R'=H
12: R=CH_3 ; R'=Ts

The successful results reported for related cyclizations in the synthesis of *Aspidosperma* alkaloids,[4] in contrast with our discouraging experiments, led us to consider that some structural factors could account for the different behavior of both series. In fact, molecular models allow to observe a larger

distance between the potential electrophilic carbon atom and the indole 3-position in the *Strychnos* than in the *Aspidosperma* series, specially when the exocyclic carbon atom attached to the piperidine nitrogen is sp^2 hybridized (carbonyl carbon atom). By this reason we turned our attention to properly functionalized tetracyclic substrates in which the exocyclic carbon linked to the piperidine nitrogen was sp^3 hybridized. In this case the distance between the indole 3-position and the potential electrophilic carbon atom was observed to be more favorable for bond formation.

In order to prove the above statement we decided to study the cyclization of a thionium ion generated by treatment of dithioacetals 15 and 16 with dimethyl(methylthio)sulfonium fluoroborate (DMTSF).[12] As it has been recently reported, DMTSF is an excellent initiator to generate thionium ions in very mild conditions.[13] However, to our knowledge there are no precedents of cyclizations on aromatic nucleus of thionium ions generated by DMTSF treatment of dithioacetals.

Dithioacetals 15 and 16 were prepared, as depicted in the following scheme, from the acetal 13, which was obtained by alkylation of the tetracyclic amine 2 with bromoacetaldehyde diethylacetal (dioxane, reflux, Na_2CO_3). Ethoxy groups were exchanged by methylthio by treatment with an excess of methanethiol (CH_2Cl_2, $BF_3.Et_2O$).



13: R=H
14: R=Ts
15: R=H
16: R=Ts
17

As expected, when dithioacetal 15 was allowed to react with DMTSF (1.3 eq, CH_2Cl_2, -10ºC to r.t., 3 h) the desired pentacyclic compound 17 was obtained in 25% yield (not optimized).[14] However, it is worth commenting that a similar treatment from dithioacetal 16, in which the indole nitrogen atom is protected by the tosyl group, failed to give any cyclization product. Only the aldehyde resulting from hydrolysis of the intermediate thionium ion was detected by ^1H-NMR spectroscopy. This result probably reflects the deactivating effect towards cyclization exerted by the tosyl group.

The extension of that procedure to the synthesis of pentacyclic *Strychnos* indole alkaloids is in progress.

ACKNOWLEDGEMENT. We are indebted to the Comisión Asesora de Investigación Científica y Técnica for financial support (project number 3229/83).

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8. Compounds 7, 8 and 9 were isolated as diastereomeric mixtures.
9. This intermediate was detected by H^1-nmr: two singlets, at δ6.23 and 6.36, due to the methine proton adjacent to the carbonyl group were observed for the two possible diastereomers.
10. For mechanistic considerations about formation of thioacetals from sulfoxides under Pummerer-type conditions, see: T.D. Harris and V. Boekelheide, *J. Org. Chem.*, 1976, *41*, 2770.
11. In the absence of Et_3N a complex mixture was obtained.
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14. 17: Ir ($CHCl_3$, cm^{-1}): 1565 (C=N). ^{1}H-nmr ($CDCl_3$, δ): 1.06 (dm, J=14 Hz, 1H, H-14α), 1.60 (s, 3H, SCH_3), 1.63 (ddd, J=14, 3.5 and 3 Hz, 1H, H-14β), 1.81-1.95 (c.s., 2H, H-20ax and H-20eq), 2.50 (br.s., 1H, H-15eq), 2.75 (dd, J=15 and 2 Hz, 1H, H-16β), 3.08 (t, J=12 Hz, 1H, H-5α), 3.13 (dd, J=15 and 10.5 Hz, 1H, H-16 α), 3.19-3.05 (masked, 1H, H-21ax), 3.34 (ddd, J=12, 5.5 and 2 Hz, 1H, H-21eq), 3.50 (dd, J=12 and 6 Hz, 1H, H-5β), 3.93 (br.s., 1H, H-3eq), 4.08 (dd, J=12 and 6 Hz, 1H, H-6α), 7.22 and 7.37 (2t, J=7.5 Hz, 2H, H-10 and H-11), 7.44 and 7.55 (2d, J=7.5 Hz, 2H, H-9 and H-12). ^{13}C-nmr ($CDCl_3$, δ): 15.26 SCH_3, 27.31 C-14, 28.33 C-15, 30.58 C-20, 31.12 C-16, 45.46 C-21, 47.67 C-6, 64.47 C-5, 70.19 C-3, 119.88, 124.05, 124.78, 128.32, 189.61 C-2. MS, m/e (relative intensity): 286 (M^++2, 8), 285 (M^++1, 19), 284 (M^+, 76), 269 (7), 237 (100), 226 (53), 194 (34), 156 (40), 95 (83).

(Received in UK 29 July 1985)