A New Strategy for the Synthesis of Pentacyclic *Strychnos* Alkaloids: Synthesis of (±)-Tubifolidine

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The hexahydro-1,5-methanoazocino[4,3-*b*]indole (**2a**) was converted into (±)-tubifolidine (**6a**) *via* a four-step synthetic sequence which involves cyclization of a thionium ion upon the 3-position of a 2,3-disubstituted indole as the crucial step.

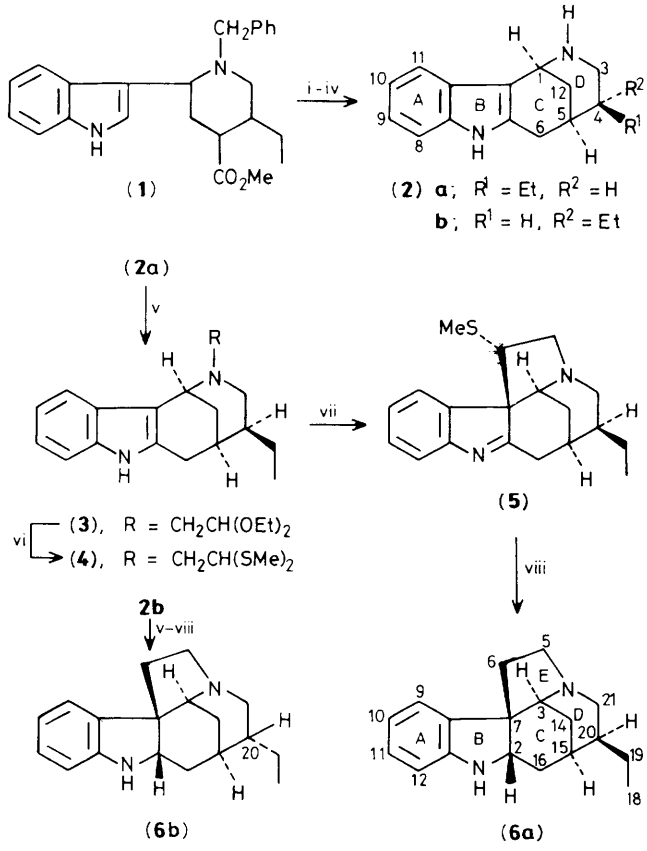
Pentacyclic *Strychnos* indole alkaloids remain one of the groups of indole alkaloids that have received little attention from a synthetic standpoint.[1] To date all syntheses reported for these alkaloids involve a transannular cyclization in the key step with simultaneous formation of the C and E rings from tetracyclic intermediates having the ring skeleton of stemmadenine.[2] This strategy was used by Harley-Mason in the first total synthesis of the pentacyclic *Strychnos* alkaloid tubifolidine (**6a**).[3] Subsequent syntheses of this alkaloid all converge to intermediates employed by Harley-Mason.[4]

We report here a completely different strategy for synthesis of the pentacyclic ring system of *Strychnos* alkaloids, which has been successfully applied to the synthesis of (±)-tubifolidine (**6a**). In this synthesis the crucial step is the closure of the five membered E ring by cyclization at the indole 3-position by an appropriately *N*-substituted 1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole system that embodies rings ABCD of the alkaloid.

A diastereomeric mixture of indolylpiperidines (**1**), obtained as previously reported,[5] was converted into an almost equimolecular mixture of epimeric derivatives (**2a**) and (**2b**) (*ca.* 30% overall yield) by saponification, cyclization with polyphosphoric acid (PPA), lithium aluminium hydride reduction of the resulting 2-acylindole, and, finally, hydrogenolysis of the benzyl group over Pearlman's catalyst.† Although the epimers could be separated after the cyclization step, this was more efficiently accomplished from the mixture of secondary amines (**2a**) and (**2b**). These isomers were easily distinguishable from their spectroscopic data. Thus, in the ^{1}H n.m.r. spectrum of (**2b**) the methylene protons of the axial ethyl side chain appear further downfield (δ 1.5—1.9) than in those of (**2a**) (δ 1.1—1.3), owing to the anisotropic effect of the piperidine nitrogen lone pair. On the other hand, in the ^{13}C n.m.r. spectrum of (**2b**) C-12 (δ 30.66) is shielded as compared with (**2a**) (δ 34.24) due to a γ effect induced by the axial ethyl group.

Construction of the five membered E ring of tubifolidine (**6a**) was accomplished by integration of a suitably functionalized two carbon unit on the piperidine nitrogen and further cyclization at the substituted indole 3-position. As previously

† Satisfactory spectral (i.r., ^{1}H n.m.r. and/or ^{13}C n.m.r.) and analytical data (elemental analyses or high resolution mass spectra) were obtained for all new compounds.



Scheme 1. *Reagents and conditions*: i, 4% aqueous $Ba(OH)_2$–dioxane (1 : 1), 80 °C, 18 h; ii, PPA, 85 °C, 1 h; iii, $LiAlH_4$, dioxane, reflux, 17 h; iv, H_2–$Pd(OH)_2$, MeOH; v, $BrCH_2CH(OEt)_2$, $NaCO_3$, dioxane, reflux, 15 h; vi, MeSH, BF_3·Et_2O, CH_2Cl_2, 0 °C, 48 h; vii, $[Me_2SSMe]^+BF_4^-$, CH_2Cl_2, 0 °C, 2 h; viii, Raney nickel, EtOH, reflux, 7 h.

described,[6] electrophilic cyclization of a thionium ion generated by treatment of a dithioacetal with dimethyl(methylthio)sulphonium fluoroborate (DMTSF) proved to be the method of choice for closure of the E ring in a related model structure. DMTSF is an excellent initiator for generation of thionium ions under very mild conditions,[7] compatible with the unprotected indole ring.

Compound (**2a**), having the same relative configuration at C-4 as tubifolidine (**6a**) has at the corresponding position (C-20),[8] was alkylated with bromoacetaldehyde diethylacetal to give (**3**). Careful exchange of ethoxy groups by methylthio was effected in 74% yield by treatment of (**3**) with an excess of methanethiol. When a mixture of the resulting dithioacetal (**4**) in methylene chloride at 0 °C was treated with DMTSF, the pentacyclic compound (**5**) was obtained in 50% yield [i.r. ($CHCl_3$) 1565 cm^{-1} (C=N); u.v. (Et_2O) λ_{max} 253 nm (indolenine)]. The ^1H n.m.r. spectrum (200 MHz) of (**5**) clearly showed that cyclization had occurred. The most significant signals were a singlet at δ 1.58 attributable to the MeS protons, a broad singlet at δ 3.88 for 3α-H, and three signals at δ 4.00 (1 H, dd, *J* 11.5 and 6.0 Hz), 3.46 (1H, dd, *J* 11.5 and 6.0 Hz), and 3.04 (1 H, t, *J* 11.5 Hz), corresponding to 6β-H, 5α-H, and 5β-H, respectively. The relative configuration at C(6), depicted in (**5**), was established on the basis of the upfield shift observed for the methylthio group rigidly held over the aromatic ring. Finally, Raney nickel treatment brought about both desulphurization and simultaneous reduction of the carbon–nitrogen double bond of tetracycle (**5**) to give (±)-tubifolidine (**6a**) (20% yield).‡ Through a similar four-step sequence (*i.e.*, alkylation, exchange by methylthio, cyclization, and reduction), tetracycle (**2b**) was converted into (±)-20-epitubifolidine (**6b**).

With methods available for the construction of the tetracyclic ABCD ring substructure of *Strychnos* alkaloids that allow the introduction of the functionalized one carbon substituent at C-6 and the ethylidene group at C-4,[9] (C-16 and C-20, respectively, in the biogenetic numbering) the strategy developed here can provide a new general synthetic entry to pentacyclic *Strychnos* alkaloids.

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‡ Spectral data for (**6a**): ^1H n.m.r. (300 MHz, $CDCl_3$) δ 7.00—6.95 (2 H, m, 9- and 11-H), 6.69 (1 H, t, *J* 8.0 Hz, 10-H), 6.56 (1 H, d, *J* 8.0 Hz, 12-H), 3.56 (1 H, dd, *J* 9.5 and 7.5 Hz, 2β-H), 3.30 (1 H, t, *J* 3.0 Hz, 3α-H), 3.11 (1 H, ddd, *J* 12.0, 10.0, and 8.5, 5α-H), 3.00 (1 H, m, 21α-H), 2.76 (1 H, ddd, *J* 12.0, 8.5, and 3.0 Hz, 5β-H), 2.33 (1 H, dt, *J* 13.5 and 8.5 Hz, 6β-H), 2.10 (1 H, t, *J* 12.0 Hz, 21β-H), 1.40—1.15 (2 H, m, 19-H), 0.84 (3 H, t, *J* 7.0 Hz, 18-H); ^{13}C n.m.r. (75 MHz, $CDCl_3$) δ 149.20 (C-13), 133.78 (C-8), 127.60 (C-11), 122.10 (C-9), 119.00 (C-10), 109.50 (C-12), 65.96 (C-2), 62.51 (C-3), 55.00 (C-21), 54.18 (C-5), 52.63 (C-7), 42.45 (C-6), 40.25 (C-20), 32.64 (C-16), 28.21 (C-14), 27.04 (C-15), 25.40 (C-19), 11.35 (C-18); *m/z* 268 (M^+), 240, 199, 144, 143, 139, 138 (100%), 130, 124, 115, 110.