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Synthetic Studies on Indole Alkaloids. VI[1] Synthesis of Tetrahydroakuammicine and Dihydrocorynantheol *via* 2-(3-Indolyl)-4-piperidones

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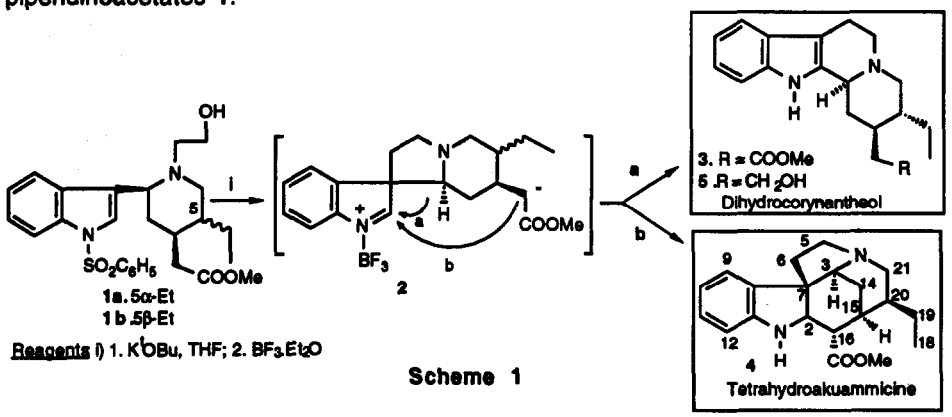
Abstract – The synthesis of dihydrocorynantheol (**5**) and of the pentacyclic *Strychnos* alkaloid tetrahydroakuammicine (**4**) is reported from 5-ethyl-*N*-hydroxyethyl-2-(1-phenylsulfonyl-3-indolyl)-4-piperidineacetates (**1**) by means of a $K^tOBu/BF_3.Et_2O$ intramolecular cyclization.

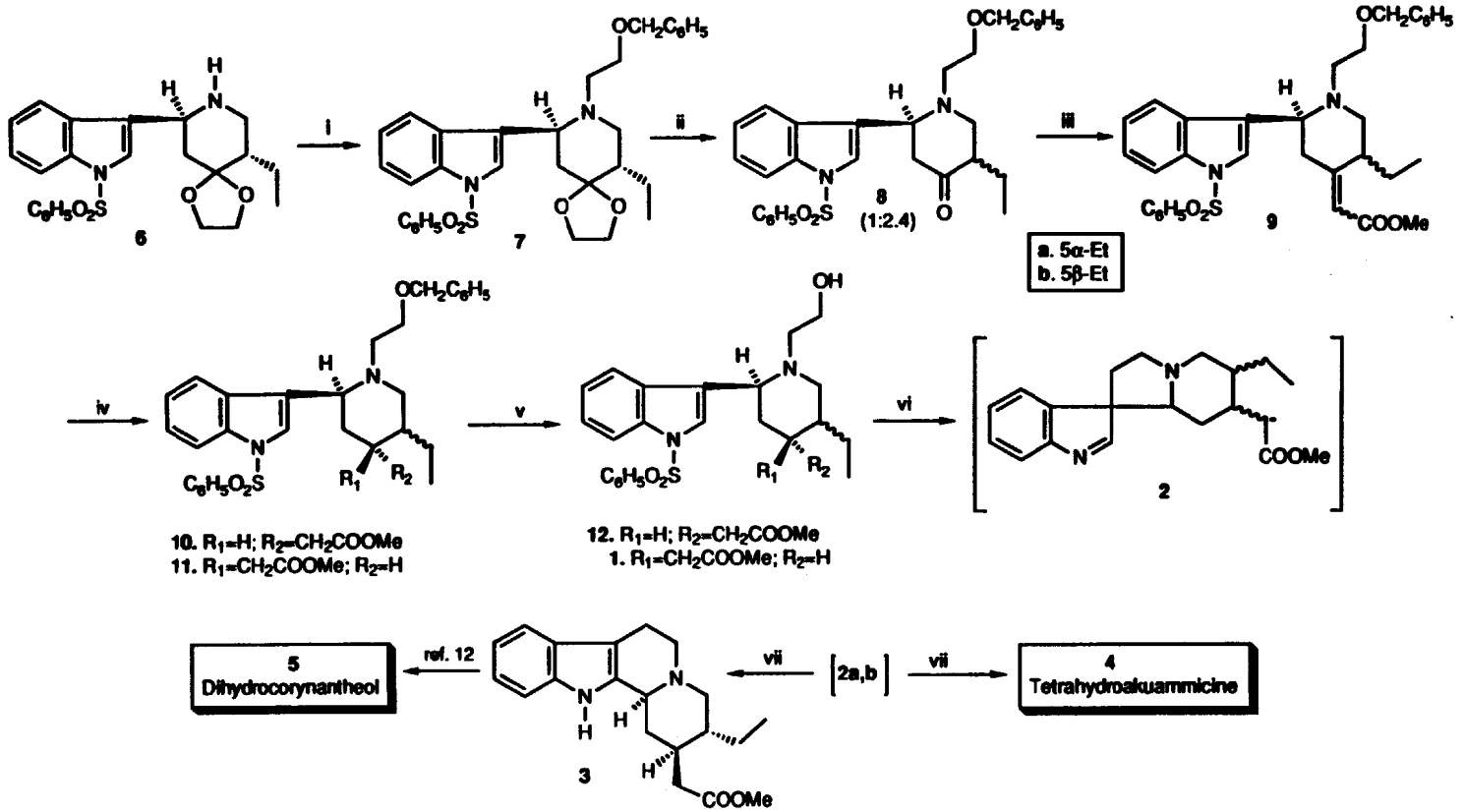
We have reported in previous papers[2] the usefulness of protected *N*-hydroxyethyl-2-(1-phenylsulfonyl-3-indolyl)-4-piperidones to obtain indolo[2,3-*a*]quinolizidin-2-ones upon treatment with two equivalents of K^tOBu. The mechanism of the process implies a displacement of the phenylsulfonyl protecting group and formation of a spiroindolenine intermediate, followed by a $BF_3.Et_2O$ induced transposition of the latter.[2b,3] More recently, we have applied the method successfully to the formal synthesis of deethyldihydrocorynantheol from methyl *N*-hydroxyethyl-2-(1-phenylsulfonyl-3-indolyl)piperidine-4-acetate.[4]

An additional interest of this approach was due to the fact that the use of three equivalents of K^tOBu followed by the action of $BF_3.Et_2O$ could provide an intramolecular cyclization of the ester enolate upon the indolenine iminium salt (Scheme 1), thus opening a remarkably direct route towards *Strychnos* indole alkaloids. We report now the last results obtained from the intramolecular cyclizations of methyl 5-ethyl-1-hydroxyethyl-2-(1-phenylsulfonyl-3-indolyl)-4-piperidineacetates **1**.



Reagents I) 1. K^tOBu, THF; 2. $BF_3.Et_2O$

Scheme 1



Reagents and conditions: i) ICH_2CH_2OBn (2 eq), K_2CO_3 (exc.), acetone, Δ, 24h (67%); ii) (1:1) 4*N* HCl-MeOH, Δ, 5h (94%); iii) NaH (1.2 eq), $(EtO)_2POCH_2COOMe$ (1.2 eq), DME, 80°C, 4h (88%); iv) H_2, 10% Pd-C, EtOH, 56 psi (97%); v) Me_2S (30 eq), $BF_3.Et_2O$ (1.1eq), CH_2Cl_2, 30°C, 18 h (83%); vi) K^tBuO (3 eq), THF, 0°C, 30 min; vii) $BF_3.Et_2O$ (2eq), Δ, 30 min (28%).

Scheme 2

Thus, alkylation of piperidine **6** (Scheme 2), prepared according to our general procedure to obtain indolylpiperidone ethylene acetals,[5] furnished the starting benzyloxyethylpiperidine **7**. Treatment of acetal **7** with 4*N* HCl in MeOH afforded a 1:2.5 mixture of piperidones **8** in 94 % yield. The minor isomer **8a** (*trans*) showed both the indolyl and the ethyl substituents in an equatorial disposition. The conformational preference of the major isomer **8b** (*cis*)[6,7] was inferred from the multiplicity and the chemical shift, in its ^{1}H-nmr spectrum, of the signal corresponding to 2-H (a triplet at δ 4.3), which reveals its equatorial disposition *syn* with respect to the nitrogen electron lone pair, and thus an axial orientation of the indolyl substituent. Treatment of **8a** with K_2CO_3 in MeOH at room temperature resulted in a partial reepimerization of the ethyl group furnishing **8b** as the major component of the equilibrium mixture. The major stability of such isomer is related to the tendency of some 2-aryl-4-piperidones to be more stable when the indolyl group is axial.[8]

A Wadsworth-Emmons reaction upon piperidone **8a** resulted in acrylate ***E*-9a** as the major product, accompanied by small proportions of ***Z*-9a** and ***E*-9b** (4:1:1). Similarly, when piperidone **8b** was submitted to the olefination process, the major resulting acrylate was ***E*-9b**, isomers ***E*-9a** and ***Z*-9a** being also detected.These results, were obviously due to the possibility of epimerization in the basic reaction conditions.[9] Hydrogenation of acrylates **9** furnished satisfactorily the corresponding acetates **10 (a,b)** and **11 (a,b)**,[10] whose debenzylation was smoothly completed with $Me_2S/BF_3.Et_2O$,[11] thus obtaining aminoalcohols **1 (a,b)** and **12 (a,b)** in yields over 80%.

At this point we chose to carry out the "$K^tOBu/BF_3.Et_2O$" reaction on compounds **1**, which presented the appropriate relative stereochemistry for both our purposes. When the reaction was assayed upon a mixture of both C-5 epimers **1** by treatment with 3 equivalents of K^tOBu in our usual reaction conditions (THF, 0°C, 30 min) followed by the addition of the Lewis acid (Scheme 2), a 1:2 mixture of **3**[12] and **4**[13] was obtained which was separated by flash column chromatography (SiO_2, 9:1 CH_2Cl_2-MeOH). Compound **4** was identified as tetrahydroakuammicine[14] by superposition of its mass spectral data with the previously reported[15] and by comparison of the ^{1}H- and ^{13}C-nmr spectra with the already described ones in the literature for 19,20-dihydroakuammicine.[16] Thus, the most significant signals in the ^{1}H-nmr were a doublet at δ 4.12 corresponding to the methine H-3 and signals at δ 6.60 and 6.75 for two of the aromatic protons characteristic of the *Strychnos* alkaloids. The epimer on C-3 of compound **3** was also detected, but not that on C-20 of tetrahydroakuammicine (**4**).

These results confirm the usefulness of our synthetic approach towards both *Corynanthe* and *Strychnos* alkaloids, thus fulfilling one of our expected goals[1] to be further developed.

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6. All compounds were characterized from their spectral data and elemental analyses.
7. **8b** (major isomer, *cis*, lower Rf) ^{1}H-nmr (200 MHz) 0.95 (t, *J*=7 Hz, 3H, CH_3), 1.45 and 1.85 (2 m, 1H each, CH_2CH_3), 2.40 (m, 1H, 5-Ha), 2.65 (dd, *J*=13 and 6 Hz, 1H, 3-Ha), 2.82 (t, *J*=5 Hz, 2H, NCH_2), 3.65 (t, *J*=5 Hz, 2H, OCH_2), 4.30 (t, *J*=6 Hz, 1H, 2-He), 4.50 (s, 2H, OCH_2), 7.15 (t, *J*=7 Hz, 1H, Ar-H), 7.25-7.50 (m, 10H), 7.85 (d, *J*=7 Hz, 3H), 8.00 (d, *J*=7 Hz, 1H, In-7H); ^{13}C-nmr 11.7, 21.7, 43.7, 50.5, 52.3, 54.4, 58.5, 69.5, 73.2, 113.7, 121.2, 123.5, 123.8, 124.0, 125.1, 126.6, 126.8, 127.5, 128.3, 129.2, 133.3, 136.0, 138.0, 208.8.
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10. It is noteworthy that no debenzylation was ever observed during the hydrogenation step.
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12. Obtention of **5** (dihydrocorynantheol) was carried out from **3** with $LiAlH_4$ (4 eq), THF, Δ, 30 min: see, Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles*, **1992**, *34*, 321-339.
13. **4**: IR 3400 (NH), 1726 (CO); ^{1}H-nmr (200 MHz) 0.90 (m, 3H, 18-H), 0.95 and 1.25 (2 m, 1H each, 19-H), 1.7-2.0 (m, 2H, 20-H and 6-H), 2.0-2.6 (m, 6H), 2.7-3.0 (m, 1H, 21-H), 3.1-3.4 (m, 2H, 5-H and 6-H), 3.73 (s, 3H, OCH_3), 4.12 (d, *J*=9 Hz, 1H, 3-H), 6.60 (d, *J*=7 Hz, 1H, 12-H), 6.75 (t, *J*=7 Hz, 1H, 10-H), 7.0-7.2 (m, 2H, 9-H and 12-H); ^{13}C-nmr 11.8 (C-18), 24.8 (C-19), 29.6 (C-14), 30.8 (C-15), 40.5 (C-20), 41.0 (C-6), 50.9 (C-21), 51.8 (OCH_3), 53.4 (C-5), 52.6 (C-16), 54.6 (C-7), 60.8 (C-3), 66.6 (C-2), 109.5 (C-12), 119.1 (C-9), 121.9 (C-10), 128.5 (C-11), 132.0 (C-8), 148.2 (C-12a), 174.8 (C=O); MS (m/z, %) 326 (M^+, 18), 295 (6), 251 (8), 217 (13), 210 (20), 199 (32), 196 (100), 182 (22), 144 (30), 130 (20), 106 (11).
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