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SYNTHETIC STUDIES ON INDOLE ALKALOIDS. III.[1] SYNTHESIS OF 1-ETHYLINDOLO[2,3-*a*]QUINOLIZIDIN-2-ONE

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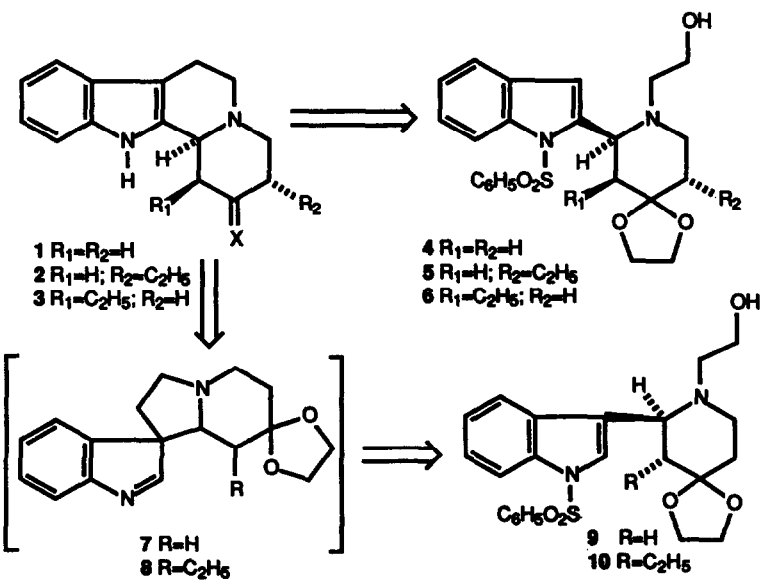
Summary: The synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one **3** is reported by potassium *tert*-butoxide cyclization of *N*-hydroxyethyl-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone ethylene acetal **10** followed by acid treatment of the intermediate spiroindolenines **8**.

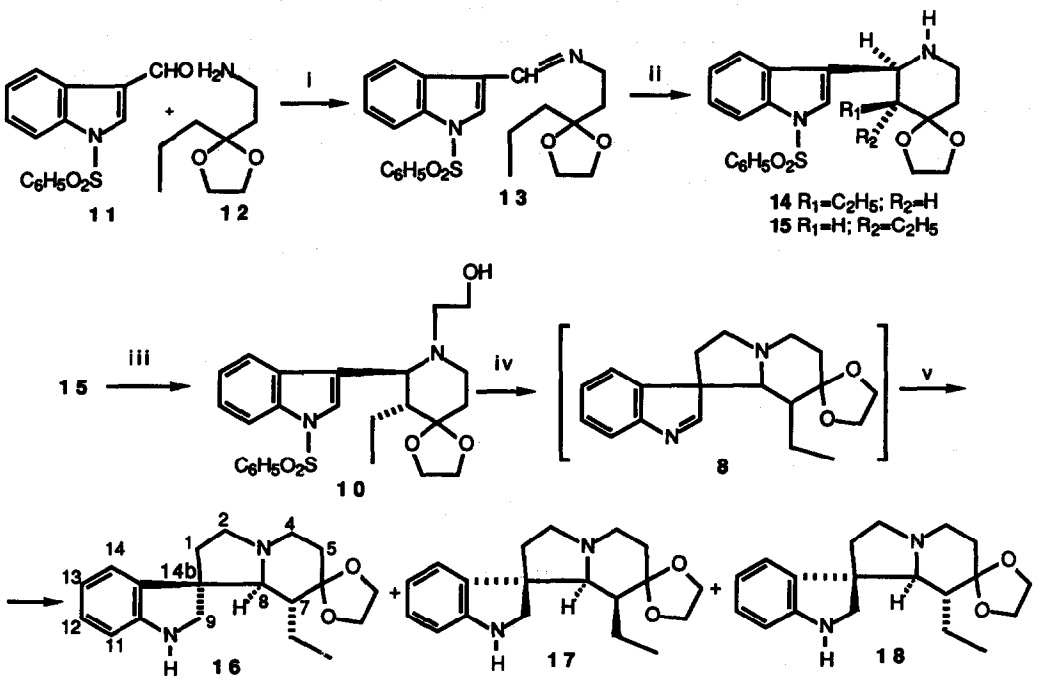
In a previous work we have reported the synthesis of 3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizidin-2(1*H*)-one (**1**)[1] and its 3-ethyl derivative **2**[2] *via* an intramolecular cyclization of hydroxyethylpiperidylphenylsulfonylindoles **4** and **5** by the action of potassium *tert*-butoxide. However, 1-ethylindolo[2,3-*a*]quinolizidin-2-one **3**, which can be considered a key intermediate in the synthesis of pentacyclic alkaloids of vincamine type,[3] has not yet been synthesized using this strategy, since the cyclization of **6** occured upon the indole nitrogen atom. We have also described[4] an improved preparation of **1** from *N*-hydroxyethyl-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone ethylene acetal (**9**) by potassium *tert*-butoxide followed by boron trifluoride-etherate and final acetal hydrolysis. The cyclization was shown to undergo through the formation of the spiroindolenine **7** which rearranges in the acidic medium.[5] We report now the successful application of the improved method to the synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one **3**.



Scheme 1

The starting hydroxyethylpiperidine **10** was prepared by alkylation of the secondary piperidine **15**, obtained by our usual method.[6] Thus, the condensation of 1-(phenylsulfonyl)indole-3-carbaldehyde **11**[7] and amino acetal **12** led to imine **13** which underwent a Mannich type cyclization on treatment with anhydrous *p*-toluenesulfonic acid, furnishing a 1:2 mixture of piperidines **14** and **15**, respectively. Rather surprisingly, only the major *trans* isomer **15** could be alkylated to **10** with 2-bromoethanol (80% yield). Treatment of **10** with potassium *tert*-butoxide (2 eq., dry THF, 0°C, 30 min) was first followed by $LiAlH_4$ reduction (2 eq., dry THF, reflux, 15 min) leading to a 2.5:2:1 mixture (45% yield) of spiroindolines **16**,[8] **17**,[9] and **18**[10], respectively. The stereochemical assignment of the major spiroindoline **16**, in which the C-9 and C-14b bond is α, corresponding to the "A series",[11] and the ethyl substituent is equatorial, was based on the ^{13}C-nmr data, wherein C-9 is more deshielded in A series (Δδ 2.5 ppm), and C-5 *c.a.* 3 ppm shielded when the ethyl chain is axial as in compound **17** due to a "γ-gauche" effect.

When the mixture of indolenine intermediates **8** were reacted with boron trifluoride-etherate (1.5 eq., 60°C, 3h) only enaminone **20**[12] was isolated in 25% yield, which was cyclized to indoloquinolizidin-2-one **3**[13], as the major product (60 % yield), by additional heating (90°C, 6 h) in aqueous sulfuric acid.[14]



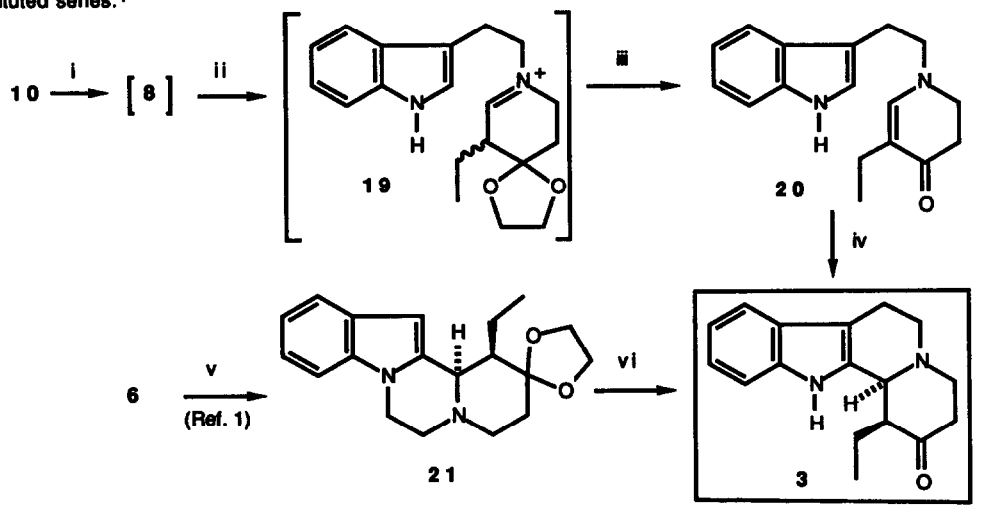
Reagents and conditions. i) Benzene, 30 min at 0°C, 6h at reflux, and 16 h Dean-Stark; ii) *p*-TsOH, benzene, reflux, 1h; iii) $BrCH_2CH_2OH$, K_2CO_3, CH_3CH_2OH, reflux, 15 h; iv) K^tBuO, dry THF, 0°C, 30 min, N_2; v) $LiAlH_4$, dry THF, reflux.

Scheme 2

The enaminone formation can be accounted for by considering that in the anhydrous acid medium the intermediates are in equilibrium with 3,4,5,6-tetrahydropyridinium salt **19**, which is transformed into enaminone **20**

during the reaction work-up. Such equilibrium would as well be consistent with the formation of the three spiroindolines **16-18** when the $LiAlH_4$ reduction is carried out. Furthermore, the major formation of **20** in comparison with the 3-deethyl enaminone from **7**,[4] would be induced by the presence of the ethyl substituent on piperidine C-3 position, which prevents the usual expected rearrangement.

On the other hand, it is worth commenting that our racemic target compound **3** was also obtained from 1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1',2':1,2]pyrazino[4,3-*a*]indole (**21**) by acetal hydrolysis and rearrangement on aqueous acid treatment (4N HCl, reflux, 4 h, 95%), and that such rearrangement had not been observed on the non-substituted series.[1]



Reagents and conditions. i) K^{t}BuO (2 eq.), dry THF, 0°C, 30 min, N_2; ii) $BF_3.Et_2O$ (1.5 eq), dry THF, 60°C, 3 h, N_2; iii) work-up; iv) 10% aqueous H_2SO_4, 90°C, 6 h; v) K^{t}BuO, 1:1 hexane-ether, 0°C, 30 min; vi) 4*N* HCl, reflux, 4h.

Scheme 3

ACKNOWLEDGEMENTS

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8. 16: ^{1}H-nmr ($CDCl_3$, 200 MHz) 0.43 (t, J=7 Hz, 3H, CH_2CH_3), 3.04 (dt, J=11, 3 Hz, 1H, 4-He), 3.53 (d, J_{AB}=10 Hz, 1H, 9-H_A), 3.65 (d, J_{AB}=10 Hz, 1H, 9-H_B), 3.82-4.04 (m, 4H, OCH_2), 6.58 (dt, J=8 , 0.5 Hz, 1H, 11-H), 6.71 (td, J=7, 1Hz, 1H, 13-H), 7.00 (td, J=8, 1 Hz, 1H, 14-H), 7.33 (br d, J=7 Hz, 1H, 12-H); ^{13}C-nmr ($CDCl_3$; 50.3 MHz) 14.2 (CH_2CH_3), 17.3 (CH_2CH_3), 34.6 (C-5), 44.6 (C-7), 48.1 (C-1), 49.3 (C-2), 53.2 (C-4), 54.1 (C14b), 61.1 (C-9), 64.2 and 64.8 (OCH_2), 76.4 (C-8), 109.3 (C-11), 111.5 (C-6), 118.7 (C-13), 125.2 (C-12), 127.6 (C-14), 135.0 (C-14a), 150.9 (C-9a).

9. 17: ^{1}H-nmr ($CDCl_3$, 200 MHz) 0.73 (t, J=7 Hz, 3H, CH_2CH_3), 3.05 (dt, J=11, 3 Hz, 1H), 3.19 (td, J=9, 4 Hz, 1H), 3.36 (d, J_{AB}=10 Hz, 1H, 9-H_A), 3.91 (d, J_{AB}=10 Hz, 1H, 9-H_B), 3.82-4.04 (m, 4H, OCH_2), 6.57 (br d, J=7.5 Hz, 1H, 11-H), 6.99 (td, J=7.5 , 1 Hz, 1H, 13-H), 7.01 (td, J=7.5, 1.2 Hz, 1H, 14-H), 7.08 (dd, J=7.5 , 1.2 Hz, 1H, 12-H) ^{13}C-nmr ($CDCl_3$; 50.3 MHz) 15.2 (CH_2CH_3), 21.9 (CH_2CH_3), 31.1 (C-5), 43.0 (C-7), 46.2 (C-1), 50.4 (C-2), 52.5 (C-4), 53.1 (C-13b), 59.2 (C-9), 64.2 and 64.4 (OCH_2), 73.2 (C-8), 109.4 (C-10), 110.5 (C-6), 118.9 (C-12), 122.7 (C-11), 127.6 (C-13), 135.5 (C-13a), 149.5 (C-9a).

10. 18: ^{1}H-nmr ($CDCl_3$, 200 MHz) 1.01 (t, J=7 Hz, 3H, CH_2CH_3), 3.49 (d, J_{AB}=10 Hz, 1H, 9-H_A), 3.67 (d, J_{AB}=10 Hz, 1H, 9-H_B), 6.67 (ddd, J=7.5, 1, 0.6 Hz, 1H, 11-H), 6.76 (td, J=7.5, 1 Hz, 1H, 13-H), 7.06 (td, J=7.5, 1.5 Hz, 1H, 14-H), 7.17 (br d, J=7.5 Hz, 1H, 12-H); ^{13}C-nmr ($CDCl_3$; 50.3 MHz) 14.4 (CH_2CH_3), 17.2 (CH_2CH_3), 34.3 (C-5), 42.3 (C-7), 47.9 (C-1), 49.4 (C-2), 52.0 (C-4), 54.2 (C13b), 56.6 (C-9), 64.3 and 64.8 (C-9), 64.3 and 64.8 (OCH_2), 72.7 (C-8), 109.2 (C-10), 110.9 (C-6), 118.5 (C-12), 122.9 (C-11), 127.7 (C-13), 135.8 (C-13a), 150.7 (C-9a).

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12. 20: IR ($CHCl_3$) 3460, 1640, 1585 cm-1; ^{1}H-nmr ($CDCl_3$, 200 MHz) 0.83 (t, J=7 Hz, 3H, CH_2CH_3), 2.00 (q, J=7 Hz, 2H, CH_2CH_3), 2.41 (t, J=7 Hz, 2H, $COCH_2$), 3.04 (t, J=7 Hz, 2H, In-CH_2), 3.40 (t, J=7 Hz, 2H, NCH_2), 3.50 (t, J=7 Hz, 2H, In-CH_2CH_2), 6.65 (s, 1H, =CH), 6.99 (s, 1H, In-2H), 7.14 and 7.18 (2t, J=7 Hz, 1H each , In-5H and In-6H), 7.39 (d, J=7 Hz, 1H, In-7H), 7.60 (d, J=7 Hz, 1H, In-4H), 8.40 (br, 1H, NH); ^{13}C-nmr ($CDCl_3$, 50.3 MHz) 14.3 (CH_2CH_3), 20.1 (CH_2CH_3), 24.9 (In-CH_2), 35.8 ($COCH_2$), 47.2 (NCH_2), 56.3 (NCH_2), 110.9 (In-3C), 111.8 (In-7C), 118.4 (In-C5), 119.5 (In-C4), 122.2 (In-C6), 123.0 (In-2C), 127.0 (In-3aC), 128.5 (=C), 136.7 (In-C7a), 153.0 (=CH), 191.0 (C=O).

13. 3: IR ($CHCl_3$) 3320, 1690 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 200 MHz) 0.77 (t, J=7 Hz, 3H, CH_2CH_3), 1.2-1.4 (m, 1H, CH_ACH_3), 1.8-2.0 (m, 1H, CH_BCH_3), 2.38 (d, J=12 Hz, 1H, 3-He), 3.68 (br s, $W_{1/2}$=7 Hz, 1H, 12b-H), 7.14 and 7.17 (2 t, J=7 Hz, 1H each, 9-H and 10-H), 7.35 (d, J=7 Hz, 1H, 11-H), 7.49 (dd, J=7 Hz, 1H, 8-H), 7.90 (br, 1H, NH); ^{13}C-nmr ($CDCl_3$, 50.3 MHz) 11.4 (CH_2CH_3), 20.3 (CH_2CH_3), 21.7 (C-7), 38.8 (C-3), 52.1 (C-6), 54.9 (C-4), 56.2 (C-1), 62.4 (C-12b), 111.2 (C-11), 118.3 (C-9), 119.7 (C-8), 121.9 (C-10), 126.6 (C-7b), 131.5 (C-11a), 136.0 (C-12a), 211.2 (C=O).

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