

SYNTHETIC STUDIES ON INDOLE ALKALOIDS. V.¹SYNTHESIS OF 2-METHYLENEINDOLO[2,3-*a*]QUINOLIZIDINES

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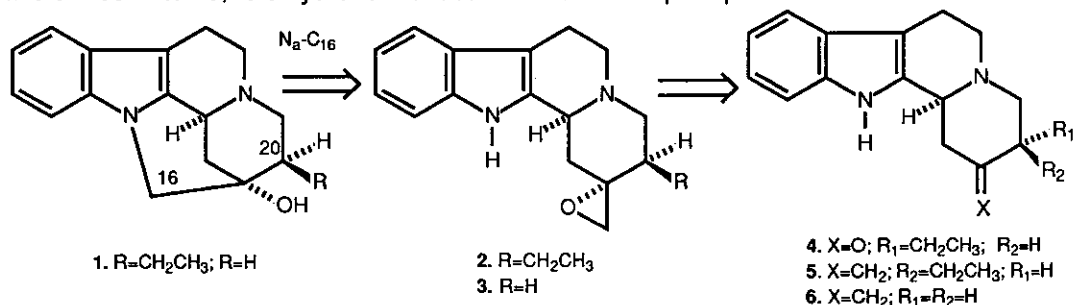
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Abstract-- A synthesis of 2-methyleneindolo[2,3-*a*]quinolizidine (6) by the intramolecular cyclization of *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidine (9) by the action of *t*-C₄H₉OK is reported.

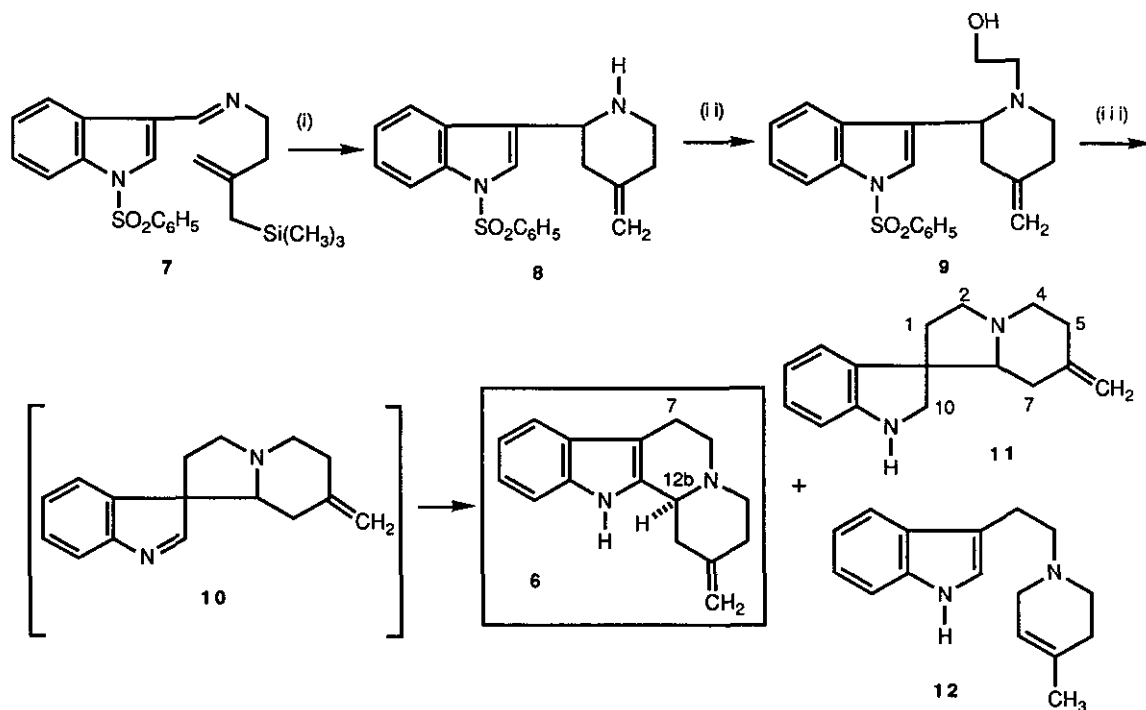
In continuing our studies on the synthesis of the C-2 functionalized indolo[2,3-*a*]quinolizidines² as a new synthetic application of 2-arylpiperidines³ we report here the direct synthesis of 2-methyleneindolo[2,3-*a*]quinolizidine (6), which can be considered a valuable intermediate of the pentacyclic normavacurine derivative (1) (R=H) *via* the epoxyindolo[2,3-*a*]quinolizidine (3) with formation of bonding between N_a and C₁₆. Thus, the transformation of indolo[2,3-*a*]quinolizidin-2-one (4) into the pentacyclic alcohol (1) (R=C₂H₅) has already been achieved through the epoxy derivative intermediate (2).⁴⁻⁶ Moreover, 2-methyleneindolo[2,3-*a*]quinolizidine (5) has been synthesized from the corresponding piperidone (4), by a standard Wittig reaction, and transformed into 19,20-dihydronormavacurine in a five step sequence.⁴



Scheme 1

The synthesis of *N*-hydroxyethylpiperidine (**9**) required for our purposes has recently been described by us from iminoallylsilane (**7**) through an intramolecular Mannich type reaction.⁷ Treatment of alcohol **9** with *t*-C₄H₉OK for 3 h at 0°C followed by reduction of spiroindolenine **10** afforded spiroindoline (**11**) only in very low yield (<5%). The presence, in the ¹H nmr spectrum, of two singlets at δ 4.75 and 4.80 corresponding to the exocyclic methylene protons and the AB system at δ 2.80 and 3.05 (*J*_{AB}=10 Hz) characteristic of 10-H in spiroindoline structures^{2c} demonstrated the formation of **11**. Structure of spiroindoline (**11**) was also evidenced by the ¹³C nmr spectrum, showing four characteristic methylene signals at low fields (δ 41.9, 52.9, 54.9, and 57.8, corresponding to C-1, C-2, C-4 and C-10, respectively).

The major product, isolated from the *t*-C₄H₉OK reaction in 82% yield, was identified as the 4-methyleneindolo[2,3-*a*]quinolizidine (**6**) from the study of its spectroscopic data.⁸ Thus, a mobile broad signal at δ 7.90 together with the aromatic signals in the ¹H nmr spectrum, clearly



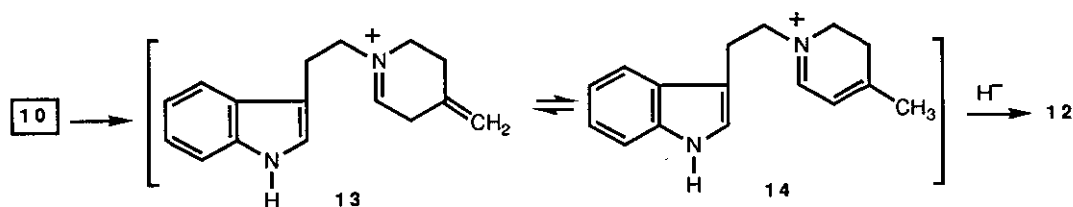
Reagents and conditions: (i) *p*-TsOH, C₆H₆, Dean-Stark, Δ, 1 h, 51%; (ii) BrCH₂CH₂OH, C₂H₅OH, K₂CO₃, Δ, 15 h, 43%; (iii) 1. *t*-C₄H₉OK, THF, 0°C, 3 h; 2. NaBH₄, THF.

Scheme 2

indicated the presence of an indole ring system, and a broad doublet ($J=11$ Hz) at δ 3.21 characteristic of the angular methine proton (12b-H) was observed. In the ^{13}C nmr spectrum, signals at δ 21.4, 60.4 and 109.4 corresponding to C-7, C-12b and the olefinic methylene, respectively, were consistent with the proposed structure for compound (6).⁹ In order to assure it, we studied the ^1H and ^{13}C nmr spectra of 6.hydrochloride, whose most relevant features were the following: (i) the indole 2,3-substitution was evidenced by the presence of two doublets (δ 7.25 and 7.38, $J=7$ Hz), and two triplets (δ 6.95 and 7.05, $J=7$ Hz) in the aromatic zone. (ii) A broad doublet ($J=10$ Hz) at δ 4.45 assignable to 12b-H showed the deshielding effect ($\Delta\delta\sim 1.2$ ppm) exerted by the piperidine nitrogen protonation.⁹

From the reaction mixture another compound was also isolated in 8% yield which was identified as *N*-(3-indolyloethyl)-1,2,5,6-tetrahydropyridine (12) from its nmr data.¹⁰ Thus, the existence of a vinylic methyl group was made evident by the presence of a singlet at δ 1.70 in the ^1H nmr spectrum, and by the signal at δ 22.8 in the ^{13}C nmr spectrum. On the other hand, the opening of ring C was clearly demonstrated by the aromatic signal at δ 7.00 (1n-2H) in the ^1H nmr, and the methine carbon at δ 122.2 in the ^{13}C nmr spectrum.¹¹ Formation of 12 was in accordance with previous observations in this series.¹ However, in this case formation of 12 was explained by an initial fragmentation followed by isomerization of the exocyclic to an endocyclic double bond, and final reduction by attack of the hydride upon C-2 (Scheme 3).

The efficient preparation of 2-methyleneindolo[2,3-*a*]quinolizidine (6) in three steps from allylsilane (7), constitutes a new formal synthesis of indole alkaloid normavacurine basic framework.



Scheme 3

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. For Part IV, see: M. Rubiralta, A. Diez, C. Vila, Y. Troin, and D. Miguel, *Heterocycles*, **1991**, *32*, 1341.
2. (a) M. Rubiralta, A. Diez, J. Bosch, and X. Solans, *J. Org. Chem.*, **1989**, *54*, 5591. (b) M. Rubiralta, A. Diez, and C. Vila, *Tetrahedron*, **1990**, *46*, 4443. (c) M. Rubiralta, A. Diez, C. Vila, Y. Troin, and M. Feliz, *J. Org. Chem.*, **1991**, *56*, 6292.
3. M. Rubiralta, P. Marco, J. Trapé, and J. Bolós, *Tetrahedron*, **1991**, *47*, 5585, and references cited therein.
4. D. D. O'Rell, F. G. H. Lee, and V. Boekelheide, *J. Am. Chem. Soc.*, **1972**, *94*, 3205.
5. For a direct synthesis of the pentacyclic C-mavacurine system by closing ring E, see: M. J. Calverley, J. Harley-Mason, S. A. Quarrie, and P. D. Edwards, *Tetrahedron*, **1981**, *37*, 1547.
6. For other synthetic entry based on the simultaneous elaboration of C and D rings, see: M. J. Calverley, B. J. Banks, and J. Harley-Mason, *Tetrahedron Lett.*, **1981**, *22*, 1635.
7. M. Rubiralta, A. Diez, D. Centeno, R. Remuson, and Y. Gelas-Mialhe, *Synth. Commun.*, **1991**, *21*, 000.
8. **6**: Ir (CHCl₃) 3474 (NH), 1662 (C=C) cm⁻¹; ¹H nmr (CDCl₃) 2.88-3.00 (m, 1H, 1-He), 2.20-2.60 (m, 1H, 1-Ha), 3.21 (br d, *J*=11 Hz, 1H, 12b-H), 4.75 (s, 2H, =CH₂), 6.95-7.10 (m, 2H, 9-H and 10-H), 7.20 (d, *J*=7 Hz, 1H, 11-H), 7.45 (d, *J*=7 Hz, 1H, 8-H), 7.90 (br, 1H, NH); ¹³C nmr (CDCl₃) 21.4 (C-7), 34.2 (C-3), 38.5 (C-1), 52.7 (C-6), 56.0 (C-4), 60.4 (C-12a), 108.5 (C-7a), 109.4 (=CH₂), 111.0 (C-11), 118.3 (C-8), 119.5 (C9), 121.5 (C-10), 127.8 (C-7b), 134.5 (C-11a), 136.1 (C-12a), 145.0 (C-2). **6**. hydrochloride: mp 268-270°C (acetone).
9. M. Rubiralta, E. Giralt, and A. Diez, "Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives", Elsevier, Amsterdam, 1991.
10. **12**: Ir (CHCl₃) 3480 (NH), 1625 (C=C) cm⁻¹; ¹H nmr (CDCl₃) 1.70 (s, 3H, CH₃), 2.00-2.30 (br s, 4H), 2.75 (t, *J*=5 Hz, 2H), 2.80 and 3.05 (2 d, *J*_{AB}=10 Hz, each 1H, 2-H), 5.45 (br s, 1H, =CH), 7.00 (s, 1H, In-2H), 7.10-7.25 (m, 2H, InH), 7.35 (d, *J*=7 Hz, 1H, In-7H), 7.65 (d, *J*=7 Hz, 1H, In-4H), 8.10 (br, 1H, NH); ¹³C nmr (CDCl₃) 22.8 (CH₃), 23.1 (In-CH₂), 30.6 (C-5), 50.4 (C-6), 52.7 (C-2), 58.9 (NCH₂) 109.6 (=CH), 111.3 (In-C7), 113.0 (In-C3), 119.0 (In-C4), 119.5 (In-C5), 121.7 (In-C6), 122.2 (In-C2), 127.0 (In-C3a), 133.1 (C-4), 136.0 (In-C7a).
11. R. Jokela, T. Tamminen, and M. Lounasmaa, *Heterocycles*, **1985**, *23*, 1707.

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