SYNTHETIC STUDIES ON INDOLE ALKALOIDS. V.[1]

SYNTHESIS OF 2-METHYLENEINDOLO[2,3-*a*]QUINOLIZIDINES

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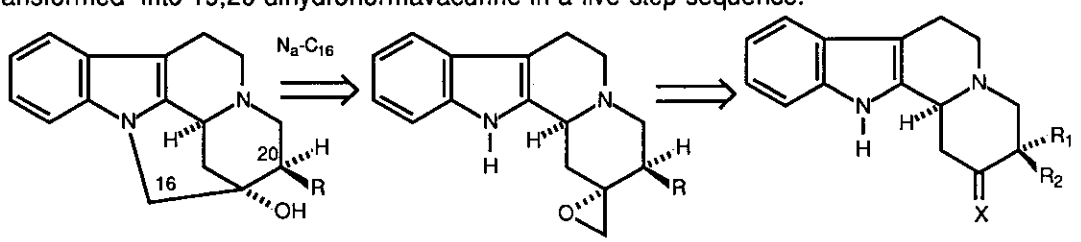
Abstract-- A synthesis of 2-methyleneindolo[2,3-*a*]quinolizidine (**6**) by the intramolecular cyclization of *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-methylenepiperidine (**9**) by the action of *t*-C_4H_9OK is reported.

In continuing our studies on the synthesis of the C-2 functionalized indolo[2,3-*a*]quinolizidines[2] as a new synthetic application of 2-arylpiperidines[3] 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 C_{16}. Thus, the transformation of indolo[2,3-*a*]quinolizidin-2-one (**4**) into the pentacyclic alcohol (**1**) ($R=C_2H_5$) 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]



1. $R=CH_2CH_3$; R=H

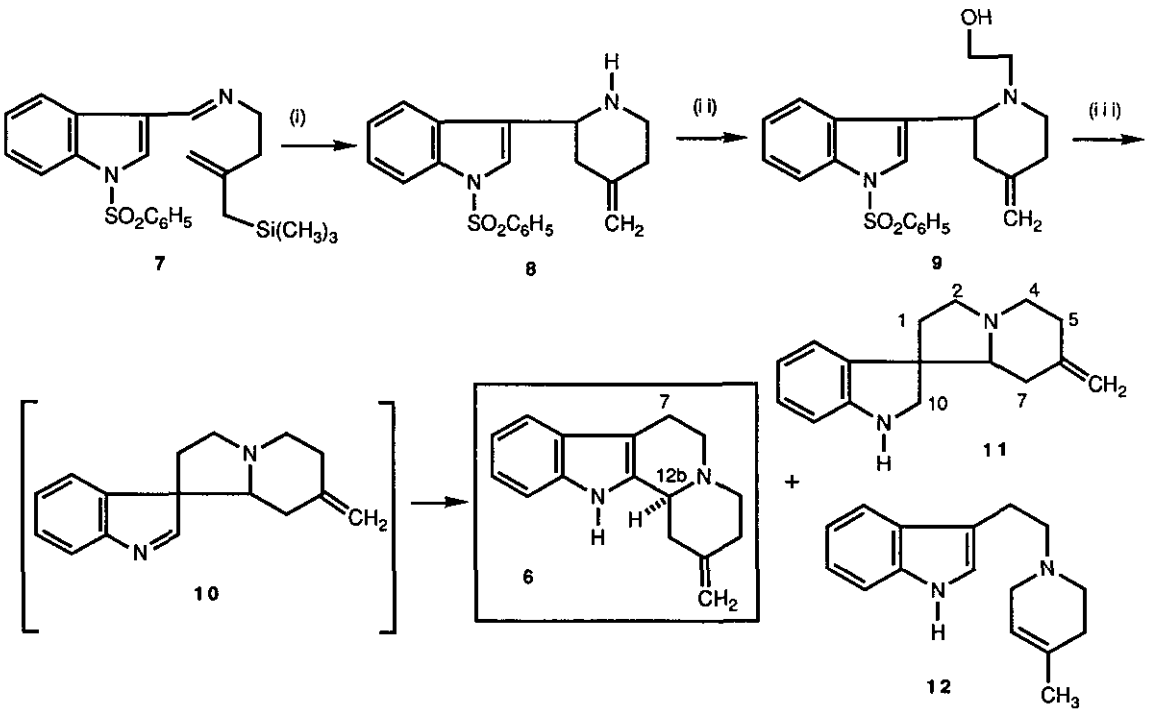
2. $R=CH_2CH_3$
3. R=H

4. X=O; $R_1=CH_2CH_3$; R_2=H
5. X=CH_2; $R_2=CH_2CH_3$; R_1=H
6. X=CH_2; $R_1=R_2$=H

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*-C_4H_9OK 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 ^{13}C 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*-C_4H_9OK 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



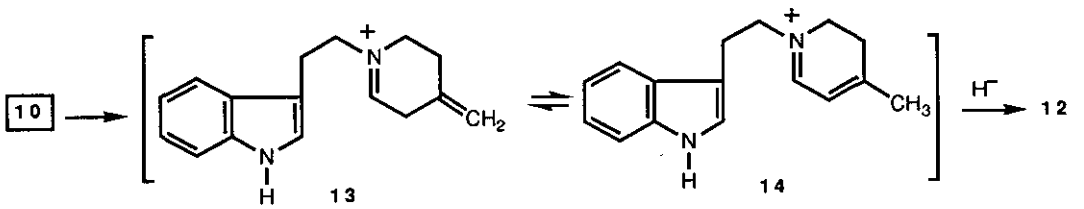
Reagents and conditions: (i) *p*-TsOH, C_6H_6, Dean-Stark, Δ, 1 h, 51%; (ii) $BrCH_2CH_2OH$, C_2H_5OH, K_2CO_3, Δ, 15 h, 43%; (iii) 1. *t*-C_4H_9OK, THF, 0°C, 3 h; 2. $NaBH_4$, THF.

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 ^{1}H 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 (Δδ~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-indolylethyl)-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 ^{1}H 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 (In-2H) in the ^{1}H 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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8. **6**: Ir ($CHCl_3$) 3474 (NH), 1662 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$) 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, $=CH_2$), 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); ^{13}C nmr ($CDCl_3$) 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 ($=CH_2$), 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).
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10. **12**: Ir ($CHCl_3$) 3480 (NH), 1625 (C=C) cm-1; ^1H nmr ($CDCl_3$) 1.70 (s, 3H, CH_3), 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); ^{13}C nmr ($CDCl_3$) 22.8 (CH_3), 23.1 (In-CH_2), 30.6 (C-5), 50.4 (C-6), 52.7 (C-2), 58.9 (NCH_2) 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).
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