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STEVENS REARRANGEMENT OF BERBINE METHIODIDES BY SODIUM BIS-(2-METHOXYETHOXY)ALUMINIUM HYDRIDE

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Stevens rearrangement of several berbine methiodides (1,2,6,9 and 11) to the spirobenzylisoquinolines (3,7, 10 and 12) and the 8-methylberbines (4,8 and 13) with sodium bis-(2-methoxyethoxy)aluminium hydride is reported. The stereochemistry at the migrating carbon and the relation between the comformation of the quinolizidinium salts and products are also described.

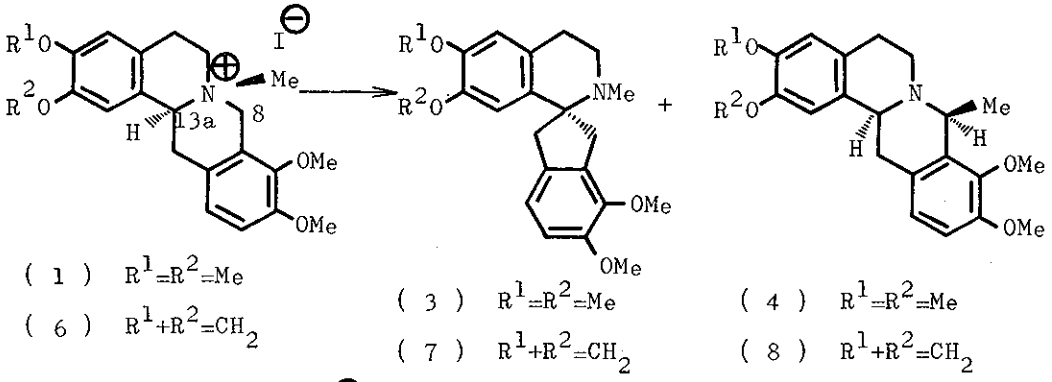
Recently we found that sodium bis-(2-methoxyethoxy)aluminium hydride effectively cleaved the C-O bond of benzyl or allyl ethers and the C-N bond of quaternary benzyl or allyl amines.[1] When berbine methiodides were heated with aluminium complex in dioxane, several unexpected products due to Stevens rearrangement were formed. Kondo's[2] and Kano's[3] groups had lately reported that treatment of quaternary berbine salts with strong bases or lithium aluminium hydride gave spirobenzylisoquinoline derivatives and the chirality at C_{13a} position of the berbine was retained during the reaction.[2]

However the stereochemistry of the migrating group and the relation between the conformation of the quinolizidinium salts and the products have not yet been studied. We here wish to report the Stevens rearrangement of berbine methiodides with sodium <u>bis</u>-(2-methoxyethoxy)aluminium hydride which revealed some stereochemical details of the reaction.

Yoshioka and his coworkers recently determined the conformation of quaternary berbine alkaloids by ^{13}C-n.m.r. spectroscopy.[4] We furthermore found that β-(±)-canadine methiodide (1),[5] having <u>trans</u> conformation as confirmed by ^{13}C-n.m.r. spectrum, showed the quaternary N-methyl group at 2.83 p.p.m. in the proton n.m.r. spectrum (DMSO-d_6), while α-(±)-canadine methiodide (2) having the <u>cis</u>-form exhibited the methyl group at 3.23 p.p.m. in the n.m.r. spectrum (DMSO-d_6). Therefore the conformation of the following quaternary berbine methiodides, used for the reactions, were determined by the chemical shift of the methyl group in the n.m.r. spectra (DMSO-d_6).

Refluxing β-(±)-canadine methiodide (1) with sodium <u>bis</u>-(2-methoxyethoxy)aluminium hydride in dioxane for 24 hr gave the spirobenzylisoquinoline (3), m.p. 117 - 118°, in 45 % yield and the 8-methylberbine (4), m.p. 152 - 153°, in 33.3 % yield. α-(±)-Canadine methiodide (2) afforded the spirobenzylisoquinoline (3) in 28 % yield and 3-(2-ethyl-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-methylisoquinoline (5),[6] m.p. 99 - 100°, in 45.1 % yield by the reaction under the same condition. The formation of the 8-methylberbine was not detected.

The spirobenzylisoquinoline (7), m.p. 135 - 137° (as hydrocholoride) and 8-methylberbine (8), m.p. 182.5 - 184°, $[\alpha]_D^{15°}$ - 235.5°



(1) $R^1=R^2=Me$

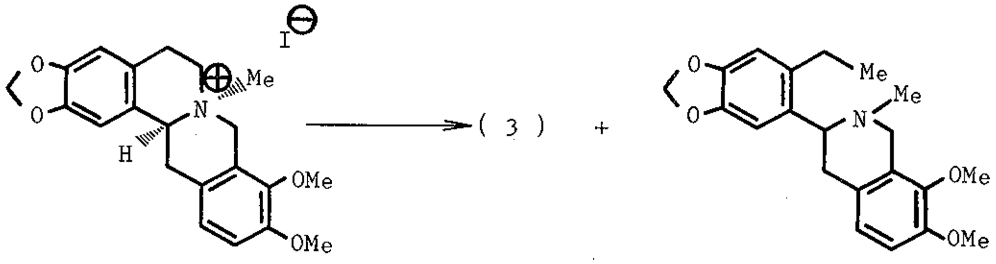
(6) $R^1+R^2=CH_2$

(3) $R^1=R^2=Me$

(7) $R^1+R^2=CH_2$

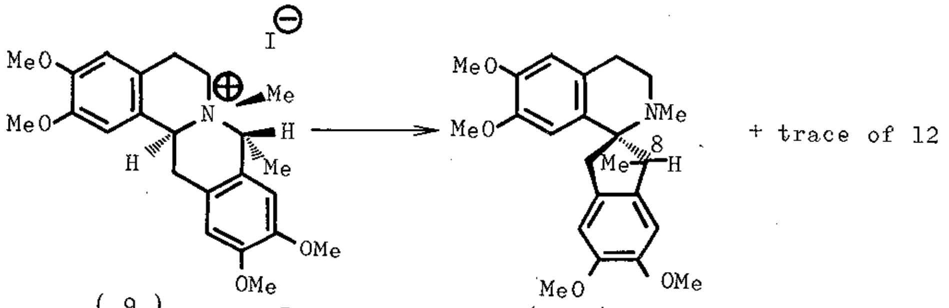
(4) $R^1=R^2=Me$

(8) $R^1+R^2=CH_2$



(2)

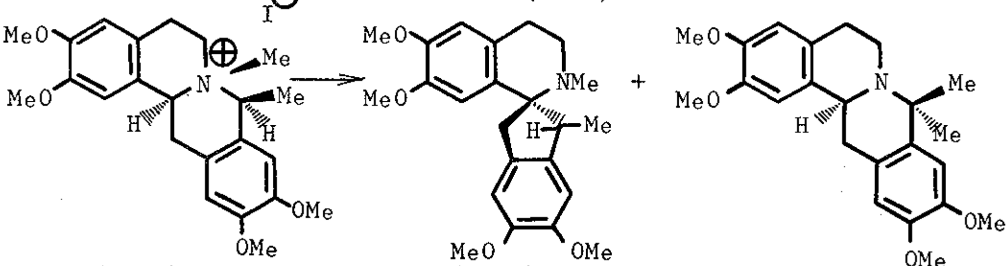
(5)



+ trace of 12

(9)

(10)



(11)

(12)
+
trace of 10

(13)

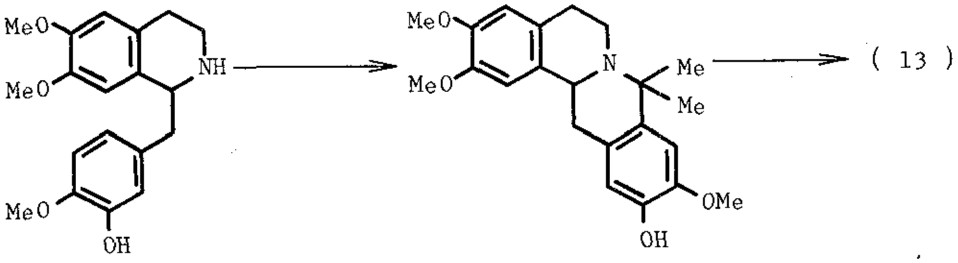
(c = 0.08, MeOH), were obtained in 39.5 and 20.2 % yield, respectively, from β-(-)-tetrahydropalmatine methiodide (6)[7] having a trans form.

The stereochemistry of the methyl group of the above 8-methylberbines (4 and 8) were confirmed to be β-oriented by spectroscopic analysis. The observation of Bohlmann bands in the i.r. spectra ($CHCl_3$) and the methyl group at 1.50 p.p.m. in the n.m.r. spectra ($CDCl_3$) is analogous with findings for coralydine.[8,9]

(±)-O-Methylcorytenchirine methiodide (9), m.p. 212 - 215° (decomp.), having trans-quinolizidine form was refluxed with the aluminium complex in dioxane for 30 hr to give the spirobenzylisoquinoline (10), m/e 315 (M^+), in 40 % yield and, in this reaction, no berbine type compound could be isolated. On the other hand, (±)-caralydine methiodide (11), m.p. 253° (decomp.), having trans-form yielded the spirobenzylisoquinoline (12), m/e 351 (M^+), in 30 % yield and the 8,8-dimethylberbine (13), m.p. 246 - 247° (decomp.) (as hydrobromide) in 10 % yield. The former spirobenzylisoquinoline (10) displayed the 8-methyl group at 0.95 p.p.m., whereas the 8-methyl group of the latter compound (12) was observed at 1.33 p.p.m. in the n.m.r. spectrum ($CDCl_3$). Based upon consideration of the effect on the chemical shift due to ring A and nitrogen, the methyl group of the spirobenzylisoquinolines (10) and (12) are anti and syn to the nitrogen, respectively. Although a trace amount of epimer was formed in each reaction, the transformation of berbine methiodides (9 and 11) into spirobenzylisoquinolines (10 and 12, respectively) proceeded stereoselectively. Therefore the stereochemistry at the migrating carbon atoms was predominantly retained. It was

was expected that [1,2]anionic shifts should proceed with inversion. However retention of configuration at the migrating atom in several examples of Stevens rearrangement had been reported.[10] This is a further example of retention of configuration.

The structure of the 8,8-dimethylberbine (13) was determined by an alternative synthesis. Thus the phenolic isoquinoline (14) hydrochloride was heated with acetone in acetic acid for 24 hr to afford the phenolic berbine (15), m.p. 160 - 161°, methylation of which with diazomethane gave 13, m.p. 246 - 247° (decomp.) (as hydrobromide).



(14) (15)

It was presumed that, in the trans-quinolizidine system, the anion firstly formed at C_{13a} position abstracted the axially oriented hydrogen at C_8 position, followed by the inversion of the anion at C_8 position and [1,2]anionic shift to give the 8-substituted berbines. The details of the above reaction mechanism should be resolved in the future.

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