

THE CHEMICAL TRANSFORMATION OF RESERPINE TO DESERPIDINE

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The partial synthesis of deserpidine 10b was achieved by the chemical transformation from reserpine 1. As a consequence of this investigation, a simple procedure for the preparation of deserpidine derivative having substituent group on the indole part has been discovered.

In the previous report,¹⁾ we described a reduction of indole alkaloids to 2,3-seco-2,3-dihydroindole alkaloids using hot mixture solution of formic acid and formamide. Le Men et al. also reported the same type reduction of the heteroyohimbine alkaloids.²⁾ In the present report, we would like to report a new partial synthesis of deserpidine 10b from reserpine 1 using the above reductive reaction.

The Nb-C5 bond cleavage reaction of 2,3-seco-2,3-dihydroreserpine 2 with trichloroethyl chloroformate (3 mol. eq.) in the presence of excess NaHCO₃ gave the urethane 3a (in 63% yield) and other byproducts, 4a (mp 63°) and Na-carbonate 5a, the latter of which reproduced 2 by reduction with Zn and acetic acid. The selective cleavage of the Nb-C5 bond is considered to give rise to a cyclopropanoindolenine 7 which then reacts with excess chloroformate to form the indole Na-carbonates 4a,b. The above assumption was supported by observation

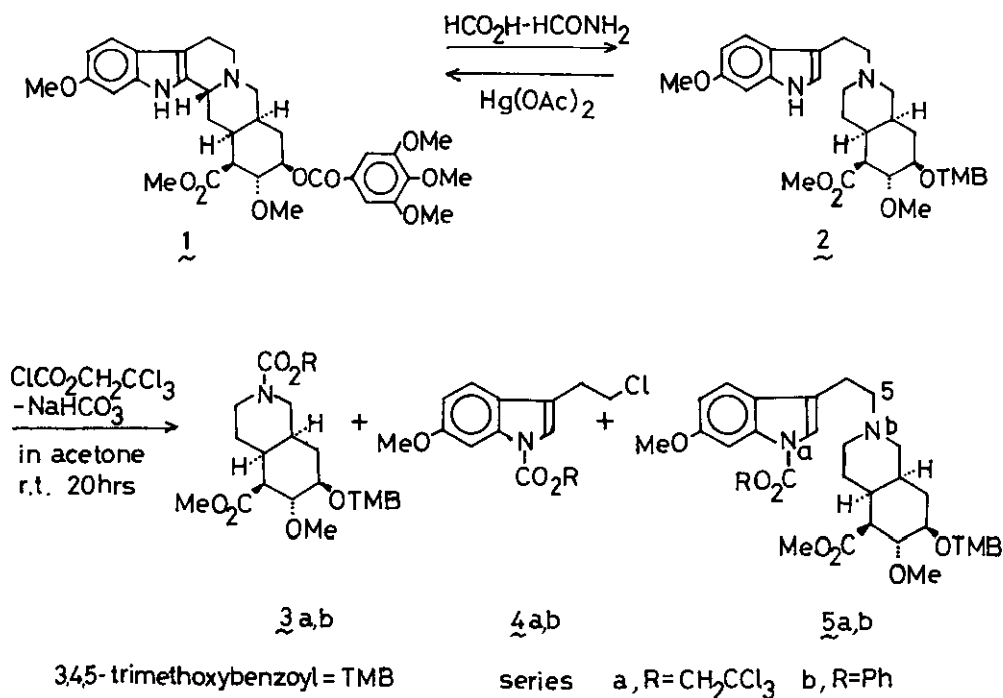


Chart 1

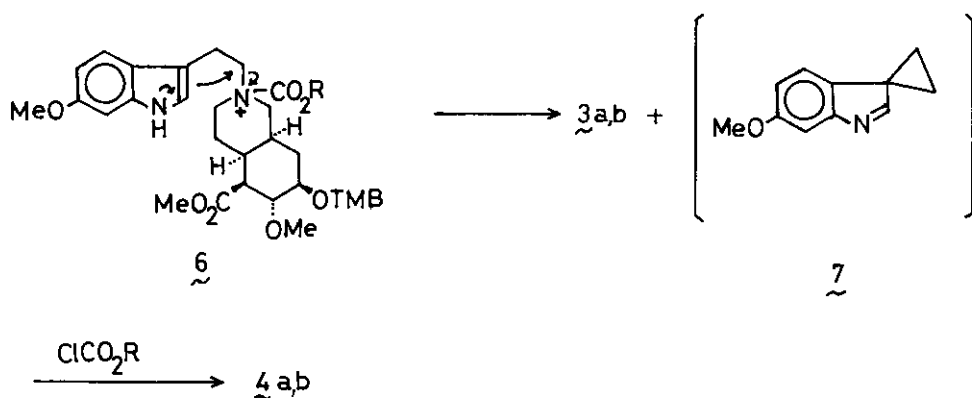


Chart 2

that 2,3-seco-2,3-dihydroreserpine Na-carbonate 5 is non reactive to the chloroformate. In the compounds 5a,b, the electron donating effect at the β -position of the indole ring is diminished by Na-acylation.

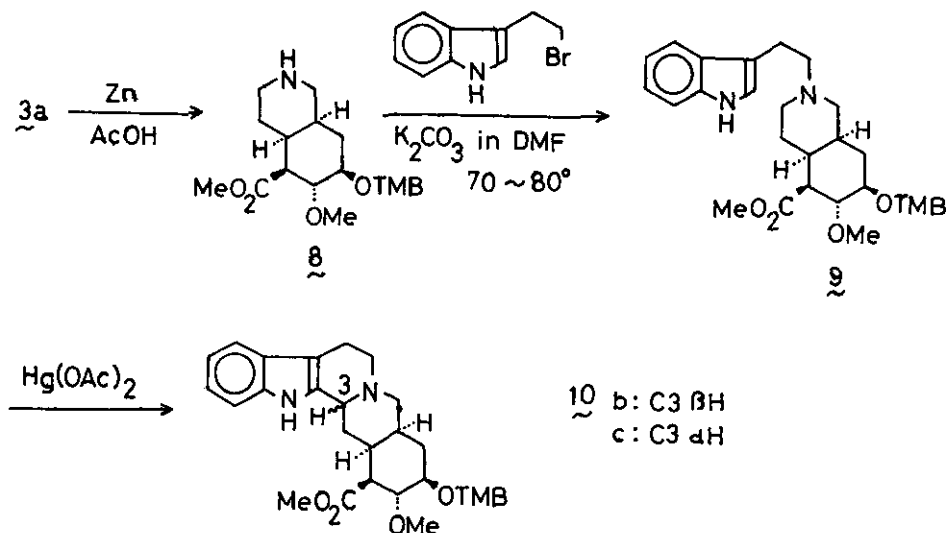


chart 3

The amorphous urethane 3a was reduced to the key compound, piperidine derivative 8 (in 85% yield), using Zn and acetic acid for 18 hrs at room temperature. The basic fraction of the reaction mixture was composed of a sole amorphous compound which showed m/e 437 (M^+ 26%), 195 (TMB^+ 100%) in the mass spectrum. The resulting piperidine derivative 8 was treated with phenyl chloroformate to give a crystalline phenyl urethane 3b (solvated with CH₂Cl₂, mp 97°). The same compound was obtained from the reaction of 2 with phenyl chloroformate. In order to synthesize the indole alkaloids, the piperidine derivative 8 and tryptophylbromide were allowed to react in the presence of K₂CO₃ powder in dimethylformamide in the usual manner.³⁾ The 2,3-seco-2,3-dihydrodeserpine 9 was obtained by this method in 64% yield. The structural

assignment for amorphous 9 was supported by uv (EtOH): 217, 273, 290 nm. ir (CHCl₃): 1740, 1720 (ester C=O). nmr (CDCl₃): 3.47-3.88 (OCH₃ x 5, s.) and mass (m/e): 580 (M⁺ 1%), 450 (100%), 195 (TMB⁺ 13%) spectra. The final stage of the deserpidine synthesis was carried out by the mercuric acetate oxidation according to Wenkert's procedure.³⁾ Two ring closed compounds, deserpidine 10b (mp 244-247°, in 14% yield) and 3-isodeserpidine 10c (amorphous, in 2% yield) were formed by the oxidation. This partially synthesized deserpidine 10b showed the identical ir spectrum compared with that of the natural product.⁴⁾ Deserpidine 10b was epimerized to 3-isodeserpidine 10c, the ir spectrum of which showed Bohlmann bands at 2770, 2820 cm⁻¹. The oxidative ring-closure reaction of 2,3-seco-2,3-dihydroreserpine 2 gave rise to reserpine 1 (in 34% yield) and isoreserpine (in 4% yield). In the case of 1, the increase in the yield is probably due to the electron donating effect of 11-methoxy group.

This procedure forms a new general method to give deserpidine derivatives having substituent groups on the indole part.

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