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 cleavege reaction of 2,3-seco-2,3-dihydroreserpine 2 with trichloroethyl chloroformate (3 mol. eq.) in the presence of excess $NaHCO_3$ 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

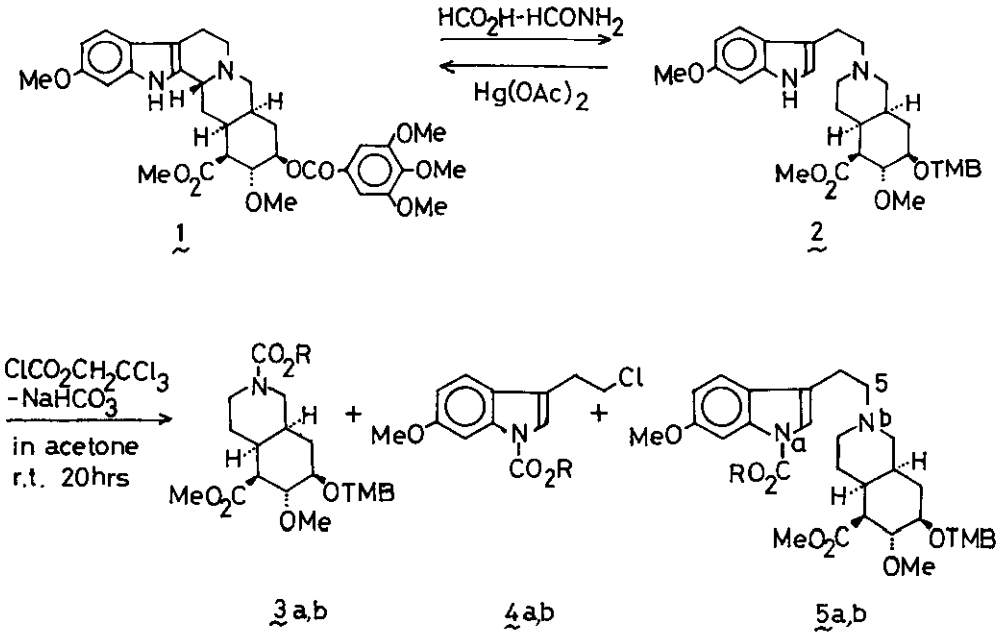

Chart 1

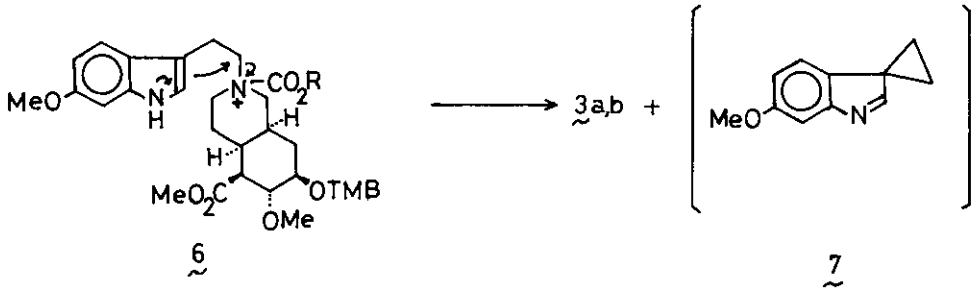

Chart 2

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.

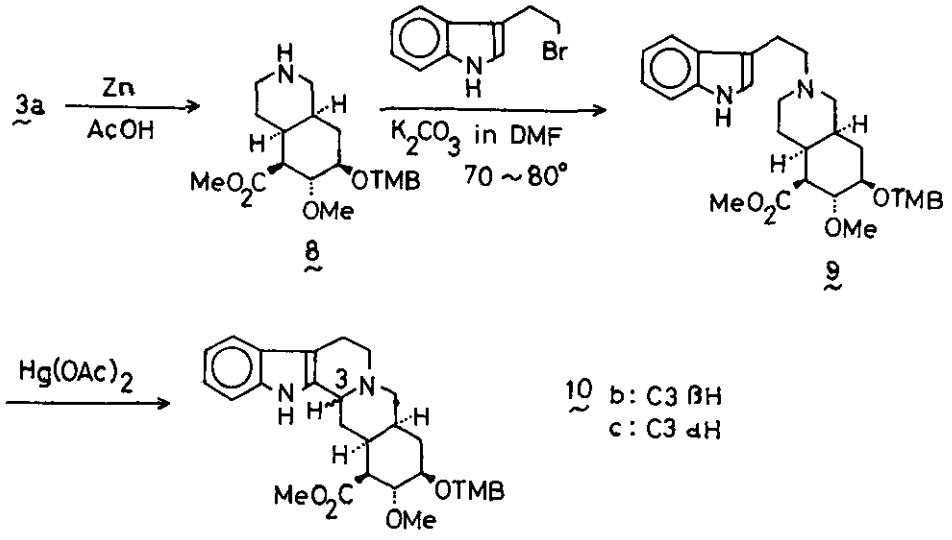

chart 3

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 CH_2Cl_2, 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 K_2CO_3 powder in dimethylformamide in the usual manner.[3] The 2,3-seco-2,3-dihydrodeserpidine 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 ($CHCl_3$): 1740, 1720 (ester C=O). nmr ($CDCl_3$): 3.47-3.88 (OCH_3 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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REFERENCES

1 S. Sakai and M. Ogawa, Chem. Pharm. Bull. (Tokyo), 1978, 26, 678.

2 F. Sigaut-Titeux, M. -J. Hoizey, L.Le Men-Olivier, J. Lévy and J. Le Men, Tetrahedron Lett., 1978, 2153.

3 E. Wenkert and B. Wickberg, J. Am. Chem. Soc. 1962, 84, 4914. ; S. Sakai, N. Aimi. J. Endo, M. Shimizu, E. Yamanaka, K. Katano, M. Kashiwazaki, M. Fujiu and Y. Yamamoto, YAKUGAKU ZASSHI, 1978, 98, 850.

4 N. Neuss, "Physical Data of Indole and Dihydroindole Alkaloids", Eli Lilly and Company, 1960.

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