THE PARTIAL SYNTHESES OF RESERPILINE AND ISORESERPILINE

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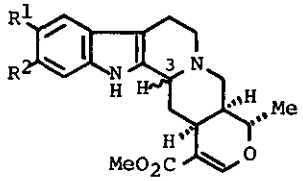
Abstract —— Reserpiline 4 and isoreserpiline 3 were first synthesized through 5,6-dimethoxyindole derivative 11, 12 and amine synthon 8 which was already derived from natural oxindole alkaloids 9, 10 and/or by the total syntheses.

In the previous paper[1] we reported the partial syntheses of heteroyohimbine alkaloids aricine 1 and reserpinine 2, through the key compound 8 which was derived by us from naturally occurring oxindole alkaloids, pteropodine 9 or isopteropodine 10 and was also synthesized by Uskoković et al.[2]



C_3-H	R^1	R^2	
α	OMe	H	aricine 1
α	H	OMe	reserpinine 2
α	OMe	OMe	isoreserpiline 3
β	OMe	OMe	reserpiline 4

Chart 1

However, by use of this route, we could not succeed to synthesize reserpiline 4 and isoreserpiline 3. This may be due to instability of the intermediating 5,6-dimethoxytryptophylbromide; the two methoxyl groups of which may raise electron density of the indole nucleus and undesired intramolecule attack of β or α carbon of indole to the halogen bearing carbon may probably prevent the compound from the normal condensation with 8. This difficulty was avoided by employing 3-(ω-chloroacetyl)-5,6-dimethoxy indole 11 and 5,6-dimethoxy-3-indole-glyoxyl chloride 12 as the intermediates.

2-(5,6-Dimethoxy-3-indolyl)-2-oxo-ethylpiperidine 13, mp 225° and 2-(5,6-dimethoxy-3-indolyl)-2,3-dioxo-ethylpiperidine 14, mp 223°[3] were obtained by the condensation between excess piperidine and compound 11 and 12 using DMF and THF

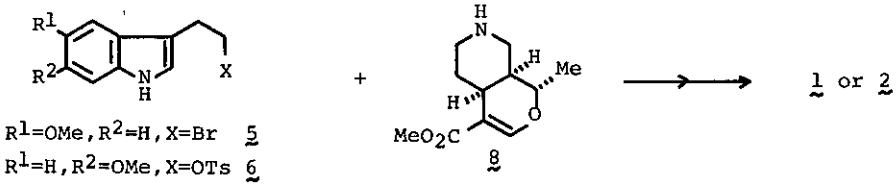
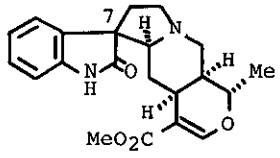


Chart 2

for the solvents respectively, in the good yields. On the reduction with $LiAlH_4$ both ketone derivatives 13 and 14 gave rise to the same 2-(5,6-dimethoxy-3-indolyl)-ethylpiperidine 15 (HCl salt mp 217-218°)[3]. However, in the case of synthesis of natural indole alkaloids which contained always a methoxycarbonyl group in the molecule, we could not use $LiAlH_4$ in above reduction steps. We used ten time equiv. mols of $NaBH_4$ and CF_3COOH in dioxane solution for the reduction reagents of 13, and redution product 15 was obtained in 47% yield.



C_7 R-form pteropodine 9
C_7 S-form isopteropodine 10

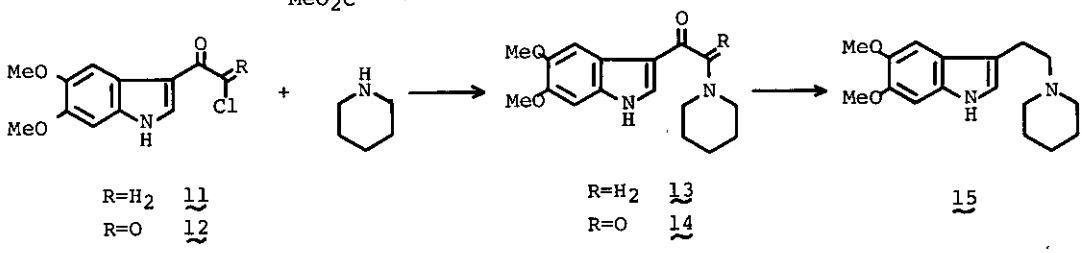


Chart 3

The ketone derivative 14 produced the mixture of BH_3-complex 16 [mp 141°, mass; m/e (%), 302(M^+, 44), 288(M^+- BH_3, 87), 98(100)] and 15 by use of excess borane-THF solution at room temperature. Without the isolation of 16, the mixture of products was refluxed with trimethylamine N-oxide in MeOH solution for the oxidative elimination of BH_3 group. This oxidative elimination of BH_3 group from N-BH_3 complex is found to be useful general method. The resulting compound 15 was produced in 80% yield by one pot reaction.

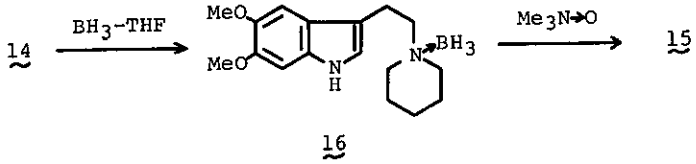
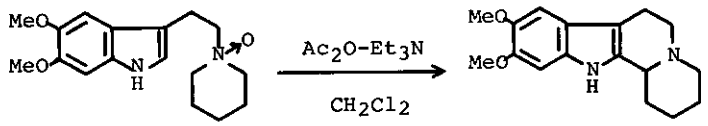


Chart 4

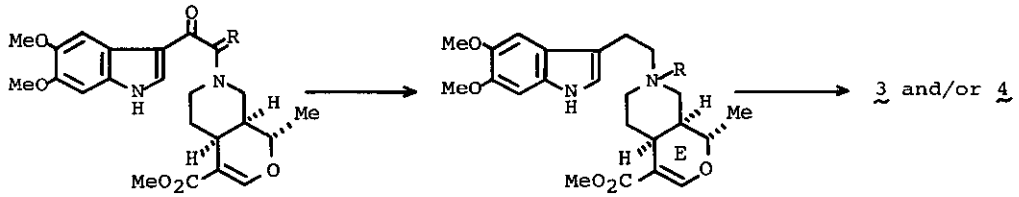
On oxidation of 2-(β-indolyl)ethylpiperidine 15 with the m-chloroperbenzoic acid, the amorphous N-oxide 17 was obtained in 97% yield. The N-oxide 17 was converted into dimethoxyindoloquinolizidine 18 (mp 178.5-180°, ir; ν_{max}^{KBr} cm^{-1}, 2850, 2800, 2750) by the use of modified Polonovsky reaction (Et_3N, Ac_2O in CH_2Cl_2, 2 hr at 0°C) in 58% yield. The same compound 18 was also obtained from 15 using $Hg(OAc)_2$ oxidation method[4] in 52% yield.



17 18

Chart 5

After the above experiments, the reaction of amine synthon 8 with 11 or 12 was carried out by the following reaction conditions. Treatment of 8 with an equiv. of 11 in anhyd-DMF with presence of powdered $NaHCO_3$ (1 equiv.) at 60°C for 3 hr gave the 6-oxo-2,3-seco-2,3-dihydroreserpiline 19 [mp 178.5-179°, m/e(%); 428(M^+, 1), 224(99), 219(100), $[\alpha]_D^{26°}$ = -7.5°($CHCl_3$)], in 72% yield. On treatment with $NaBH_4$(5.5 equiv.) and HOAc (5.5 equiv.) in dioxane solution under refluxing for 2 hr, ketone derivative 19 was converted into the corresponding 2,3-seco-2,3-dihydroreserpiline 21 [mp 129-133°, m/e(%); 414(M^+,56), 224(100), 190(27), $[\alpha]_D^{20°}$ = -42°($CHCl_3$), cd(MeOH); Δε(nm) -7.48(246)], in 72% yield.



R=H_2 19
R=O 20

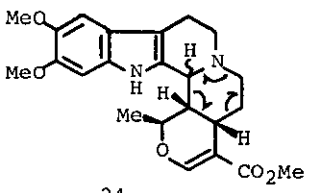
R=none 21
R=→BH_3 22
R=→O 23

Chart 6

Treatment of 5,6-dimethoxyindole with the oxalyl chloride (2 equiv. mols) in anhyd-THF at -10° gave 12, which was treated with amine synthon 8 (1.1 equiv.) at the presence of 4-dimethylaminopyridine (1 equiv.) and pyridine (10 equiv.) in anhyd-THF solution (r.t. 2 hr) to afford 5,6-dioxo-2,3-seco-2,3-dihydroreserpiline 20 [mp 226-227°, m/e(%); 442(M^+, 8), 316(22), 204(100)] in 50% yield from 5,6-dimethoxyindole. On reduction with excess borane (1M-THF solution, 9 equiv. mols, r.t., 12 hr), 20 gave the mixture of 2,3-seco-2,3-dihydroreserpiline 21 and its BH_3-complex 22. Without purification, the mixture was then treated with

trimethylamine N-oxide (4 equiv. mols) in MeOH (reflux, 9 hr) to give 21, in 49% yield.

2,3-Seco-indole derivative 21, thus obtained, was then submitted to oxidative cyclization to form the corresponding indole alkaloids as follows. A solution of 21 in 5% aq.HOAc was heated at 90°C (1.5 hr) with $Hg(AcO)_2$ (10 equiv. mols) and then treated with $NaBH_4$[4]. Extraction of the basified solution with $CHCl_3$ afforded a mixture consisting of three indole alkaloids (3, 4, 24). The least polar component 3, (mp 201.5-202°, in 19% yield), was identified with natural isoreserpiline 3 by mixed fusion and comparison of tlc, uv, ir, mass and cd spectra. Amorphous 4, in 0.3% yield, was shown to be reserpiline 4, on the basis of tlc, cd and mass spectra. Amorphous 24, obtained in 0.6% yield, was found to be an inside heteroyohimbine derivative from the mass spectrum [m/e(%); 412(M^+, 93), 411(52), 383(M^+-29, 72), 311(33), 244(65) and 230(100)] which showed the base peak at m/e 230. This retro Diels-Alder peak is diagnostic to inside heteroyohimbine type structures since the corresponding peak on the mass spectra of the normal heteroyohimbine derivative are usually weak or of medium strengths at most. The stereochemistries at C-15, C-19 and C-20 of 24 were inferred from those of compound 21. The peak at m/e 383 is also characteristic to the inside heteroyohimbine derivatives.[1]



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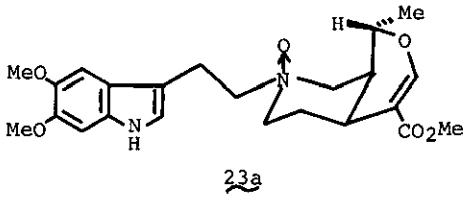
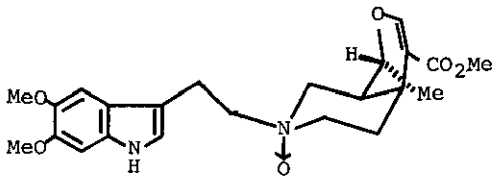
In order to increase the yield of reserpiline 4 on the above cyclization, then we employed a modified Polonovsky reaction. m-CPBA oxidation of 21 in CH_2Cl_2 gave a mixture of epimeric N-oxides, which could be separated by alumina column chromatography. The less polar N-oxide 23a, [mp 123-125°, in 66% yield, m/e(%); 430 (M^+, 0.5), 414(1.4), 203(100), nmr; δ 1.50(3H, d. J=6Hz, C-19 Me), 5.11(1H, d.q., J_1=10 Hz, J_2=6 Hz, C-19 H), cd(MeOH); Δε(nm) -4.39(232)], showed the deshielding effect (ca. 0.6ppm) at C-19 H due to N-oxide anisotropy and characteristic Cotton



23a



23b

Chart 7

effect due to the conformation of E ring containing β-alkoxyacrylic ester group.[5] Amorphous 23b, [in 2% yield, m/e(%); no M^+, 203(100), cd(MeOH); Δε(nm) +3.51 (242)] showed the Cotton curve which is antipodal to that of 23a.

The mixed N-oxides 23a,b were treated with $(CF_3CO)_2O$ in CH_2Cl_2 (-78°∿ +5°C, 2 hr) and the reaction products were purified using column chromatography (SiO_2) and preparative tlc. In this case, the three indole alkaloids, isoreserpiline 3, insideheteroyohimbine 24 and reserpiline 4 were obtained in 3.1%, in 2.5% and in 3.8% yield respectively. The partially synthesized reserpiline 4 formed HCl salt, mp 219-222° which was identical with the authentic sample in all respects.

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REFERENCES

1. S.Sakai, N.Aimi, J.Endo, M.Shimizu, E.Yamanaka, M.Fujiu, and Y.Yamamoto; YAKUGAKU ZASSHI 98 850 (1978).
2. M.R.Uskoković, R.L.Lewis, J.J.Partridge, C.W.Despreaux, and D.L.Pruess; J. Am. Chem. Soc. 101 6742 (1979).
3. Szu-Hsun Peng, Chao-Kuei Pu, Ming Hua Li, Chen-Hsiang Yang and Shih Sheng; Yao Hsueh Hsueh Pao 13 (1), 24(1966), CA. 65 3871d (1966).
4. E.Wenkert and B.Wickberg; J. Am. Chem. Soc., 84 491(1962).
5. N.Aimi, E.Yamanaka, N.Shinma, M.Fujiu, J.Kurita, S.Sakai and J.Haginiwa; Chem. Pharm. Bull. 25 2067 (1977).

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