Communications to the Editor

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THE PREPARATION OF 14-HYDROXYLATED YOHIMBINE AND RESERPINE DERIVATIVES

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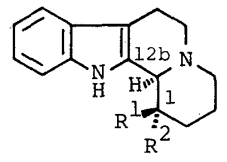
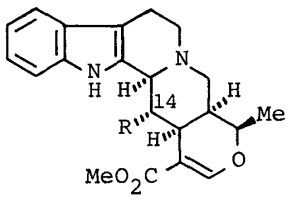
Hydroxylation at C-14 of yohimbine (6), pseudoyohimbine (7) and isoreserpine (8) was made through oxidation of the enamines (10, 15) with benzoyl or *p*-nitrobenzoyl peroxide followed by reduction with $NaBH_4$ and removal of benzoyl or *p*-nitrobenzoyl group to give the 14-hydroxylated compounds (13, 14, 22).

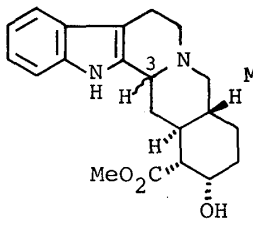
KEYWORDS—— indole alkaloid; enamine; hydroxylation; yohimbine; reserpine; benzoyl peroxide; quinolizidine

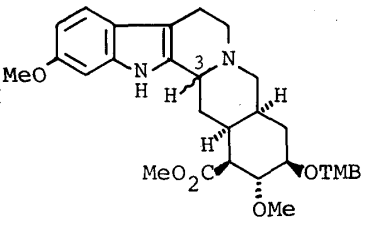
In a previous paper, we reported[2] two hydroxylation methods at C-14 (C-1 in the case of 1) of indole alkaloids using the indoloquinolizidine (1) as a starting material: *a)* oxidation of the 1,12b-dehydro derivative (enamine) with benzoyl peroxide followed by reduction with $NaBH_4$ and removal of benzoyl group to give the *cis*-alcohol (2), and *b)* hydroboration-oxidation of the enamine to give the *trans*-alcohol (3). In addition, the partial synthesis of the natural alkaloid, 14α-hydroxyrauniticine (5), from rauniticine (4) was achieved by method *b*.[2] Since indole alkaloids, yohimbine (6) and reserpine (9), are well-known as medicinal compounds, the extensibility of their bioactivities by the introduction of the 14-hydroxyl group will be widely useful. Here, we describe the application of the above hydroxylation method *a)* to yohimbine (6) and reserpine (9) to give the 14-hydroxylated compounds (13, 14, 21, 22).

Treatment of 3,14-dehydroyohimbine (10)[3] with $(PhCO_2)_2$ (1.5 eq) followed by reduction with $NaBH_4$ gave 14β-benzoyloxyyohimbine (11, 42%) and 14α-benzoyloxypseudoyohimbine (12, 5%) together with yohimbine (6, 20%) [11: $[\alpha]_D^{17}$+4.2° (MeOH); MS m/z(%): 474(M^+,16), 352(100); HCl salt: mp 225-228°C (MeOH); $[\alpha]_D^{24}$+17.3° (MeOH). 12: mp 194-195°C (MeOH); $[\alpha]_D^{29}$-202.2° (MeOH); MS m/z(%): 474(M^+,5), 352(100)].[4] The yield of the minor benzoate (12) was raised to 16% [11, 25%] when $Zn(BH_4)_2$ was used as a reducing agent. The spectral data of 11 showed the *trans*-quinolizidine structure: the presence of Bohlmann bands in the IR spectrum and the characteristic chemical shift of C-6 (δ21.3)[5] in the ^{13}C-NMR spectrum. The ^{1}H-NMR signal of H-14 (δ5.75) appeared as the broad singlet indicating *cis* arrangement of H-3 (axial) and H-14 (equatorial). The axial orientation of the benzoyloxy group was further confirmed by the observation of the upfield shift of C-16 (δ52.6→δ48.2) and C-20 (δ40.2→δ35.2) for 11 from 6 due to γ-*gauche* effect (Table). On the contrary, the spectral data of 12 showed the *cis*-quinolizidine structure: the absence of Bohlmann bands in the IR spectrum,







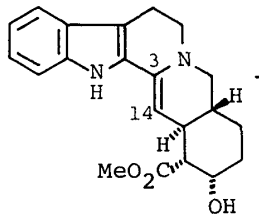


1: $R^1=R^2=$ H
2: $R^1=$ OH, $R^2=$ H
3: $R^1=$ H, $R^2=$ OH

4: R= H
5: R= OH

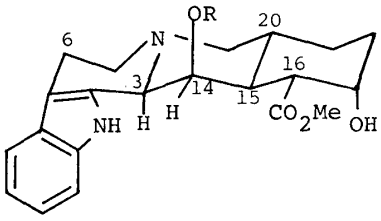
6: 3α-H
7: 3β-H

8: 3α-H
9: 3β-H

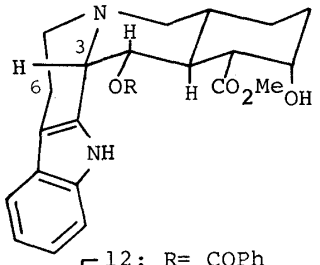


10

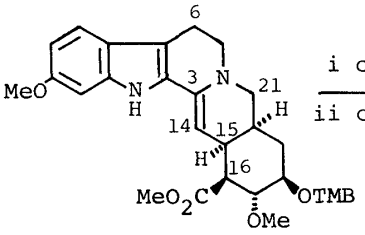
i
ii or iii



iv → 11: R= COPh
iv → 13: R= H

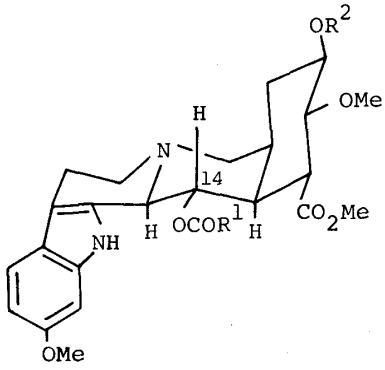


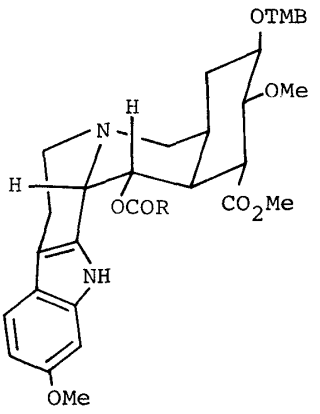
iv → 12: R= COPh
iv → 14: R= H



15

i or v
ii or iii

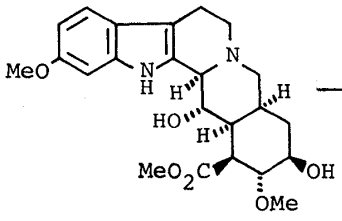




iv → 16: $R^1=$ Ph, $R^2=$ TMB
iv → 18: $R^1=$ Ph, $R^2=$ H
19: $R^1=C_6H_4$-$p$$NO_2$, $R^2=$ TMB

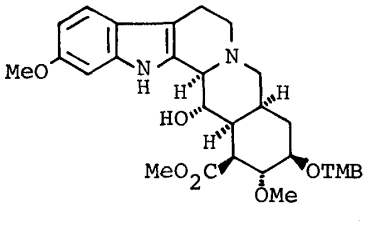
17: R= Ph
20: R= C_6H_4-$p$$NO_2$

19 —iv→



21

—vi→



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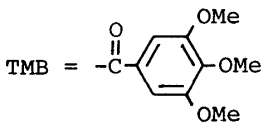
TMB = 

i) $(PhCO_2)_2$ ii) $NaBH_4$ iii) $Zn(BH_4)_2$ iv) NaOMe
v) $(pNO_2C_6H_4CO_2)_2$ vi) TMBCl/DMAP/pyridine

Table. ^{13}C Chemical Shifts of Yohimbine and Reserpine Derivatives[a)]

Carbon	Yohimbines						Reserpines								
	6[b)]	11	13	7[c)]	12[d)]	14	8[b)]	16	18	19	21	22	9[b)]	17	20
3	59.8	64.2	64.5	54.1	57.2	59.6	59.6	64.5	64.5	64.3	65.1	65.0	53.6	57.2	57.5
6	21.5	21.3	21.5	16.7	17.2	16.6	21.6	22.0	22.0	22.1	21.8	21.8	16.7	17.0	17.2
14	33.8	67.8	67.5	31.5	77.4	75.0	27.6	71.8	71.9	73.1	70.1	70.2	24.1	70.7	71.9
15	36.4	40.4	41.4	31.9	37.1	38.6	37.0	44.1	44.7	43.9	46.6	46.2	32.2	37.6	37.5
16	52.6	48.2	48.1	51.8	49.8	50.0	51.7	50.3	50.0	50.4	50.6	50.9	51.6	50.2	50.1
20	40.2	35.2	34.4	39.4	39.7	38.9	34.6	36.3	36.6	36.4	36.2	35.9	33.8	35.4	35.4
21	61.0	61.6	61.2	51.7	51.2	50.6	59.6	59.7	59.9	59.6	59.7	59.3	48.8	48.9	49.1

a) The values are in ppm downfield from Me_4Si. The spectra were measured in $CDCl_3$ unless otherwise stated. b) Values from ref. 5. c) values from ref. 9. d) In CD_2Cl_2 solution.

^1H-NMR signal of H-3 at δ4.78 in the downfield position[6] and ^{13}C-NMR signal of C-6 at δ17.2 in the upfield position.[5] The equatorial orientation of the benzoyloxy group was confirmed by analysis of the coupling pattern of H-14 (δ5.44,dd,$J_{14,15}$ =11Hz,$J_{3,14}$=5Hz) showing the diaxial arrangement of H-14 and H-15.

Treatment of 11 with NaOMe in refluxing MeOH gave 14β-hydroxyyohimbine (13) [80%; mp 155-158°C(MeOH-H_2O); $[\alpha]_D^{17}$+10.9°(MeOH); MS m/z(%): 370(M^+,100); ^1H-NMR δ: 3.40(br s,H-3), 3.98(br s,H-14)].[7] The ester exchange of 12 occurred at room temperature to give 14α-hydroxypseudoyohimbine (14)[80%; $[\alpha]_D^{22}$-80.8°(MeOH); MS m/z(%): 370(M^+,100); ^1H-NMR δ: 4.48(m,H-3)].[7]

In the case of reserpine (9), the hydroxylation gave much different results from yohimbine (6). 3,14-Dehydroreserpine (15) was prepared in the usual manner.[3,8] Treatment of the enamine (15) with $(PhCO_2)_2$—$NaBH_4$ gave 14α-benzoyloxyisoreserpine (16,36%) and 14α-benzoyloxyreserpine (17,5%)[16: mp 147°C(MeOH-H_2O); $[\alpha]_D^{29}$-135.3°($CHCl_3$); MS m/z(%): 728(M^+,1), 606(62), 212(100); ^1H-NMR δ: 3.52(H-3), 5.77(t,J=10Hz,H-14). 17: mp 196°C(MeOH); $[\alpha]_D^{29}$-162.9°($CHCl_3$); MS m/z(%): 728(M^+,0.5), 212(100); ^1H-NMR δ: 4.77(d,J=5Hz,H-3), 6.09(dd,$J_{14,15}$= 11Hz,$J_{3,14}$=5Hz,H-14)]. ^1H- and ^{13}C-NMR (Table) spectral data showed the *trans*-quinolizidine structure for 16 and *cis*-quinolizidine structure for 17, respectively. The equatorial orientation of the benzoyloxy group of 16 and 17 was determined by analyses of their coupling patterns of H-3 and H-14.

Treatment of the major benzoate (16) with NaOMe in MeOH at room temperature gave methyl 14α-benzoyloxyisoreserpate (18)[84%; $[\alpha]_D^{29}$-10.8°($CHCl_3$); MS m/z(%): 534(M^+,1), 412(100); ^1H-NMR δ: 3.49(d,J=9.5Hz,H-3), 5.68(t,J=9.5Hz,H-14)].[7] In order to obtain the 14-hydroxyl compound (21), compound (18) was treated with NaOMe in refluxing MeOH to give the reaction mixture which showed several spots on TLC. Therefore, *p*-nitrobenzoyl peroxide was chosen as an oxidizing agent instead of benzoyl peroxide since the *p*-nitrobenzoyl group was removed much more easily than the benzoyl group. The enamine (15) was treated with *p*-nitrobenzoyl peroxide followed by reduction with $NaBH_4$ to give 14α-*p*-nitrobenzoyloxyisoreserpine (19,47%) and 14α-*p*-nitrobenzoyloxyreserpine (20,7%)[19: mp 209°C (MeOH); $[\alpha]_D^{31}$-122.9°($CHCl_3$); MS m/z(%): 773(M^+,1), 606(100); ^1H-NMR δ: 3.54(d, J=10Hz,H-3), 5.82(t,J=10Hz,H-14). 20: mp 228°C(MeOH); $[\alpha]_D^{31}$-228.5°($CHCl_3$);

MS m/z(%): 773(M^+,9), 606(88); ^{1}H-NMR δ: 4.73(d,J=5Hz,H-3), 6.15(dd,$J_{14,15}$=11Hz, $J_{3,14}$=5Hz,H-14)]. The stereostructures of 19 and 20 were further confirmed by analyses of ^{13}C-NMR data (Table). When $Zn(BH_4)_2$ was used as a reducing agent instead of $NaBH_4$, 19 and 20 were obtained in 19 and 9% yields, respectively. The major benzoates [16 and 19 (3α-H, 14β-H)] possessed *trans* configuration between H-3 and H-14 in the case of reserpine, while the major benzoate [11 (3α-H, 14α-H)] in the case of yohimbine possessed *cis* configuration between H-3 and H-14.

Treatment of the compound (19) with NaOMe in MeOH at room temperature gave methyl 14α-hydroxyisoreserpate (21) [52%; mp 191°C(benzene); $[\alpha]_D^{31}$-50.8°($CHCl_3$); MS m/z(%): 430(M^+,100); ^{1}H-NMR δ: 3.07(d,J=9.5Hz,H-3), 4.15(td,$J_{3,14}$=$J_{14,15}$=9.5Hz, $J_{14,OH}$=4.5Hz,H-14,changed to triplet on addition of D_2O)].[7]

The diol compound (21) was acylated with 3,4,5-trimethoxybenzoyl chloride (4 eq) in pyridine in the presence of *p*-dimethylaminopyridine (2 eq) at room temperature to give 14α-hydroxyisoreserpine (22)[58%; mp 142°C(benzene-hexane); $[\alpha]_D^{28}$-129.1°($CHCl_3$); MS m/z(%): 624(M^+,2), 212(100); ^{1}H-NMR δ: 3.13(d,J=10Hz,H-3), 4.26(t,J=10Hz,H-14,changed to the clear triplet on addition of D_2O)].[7]

Hydroxylation of the enamines (10 and 15) by hydroboration-oxidation was unsuccessful. The biological activities of the compounds obtained here are under investigation.

REFERENCES AND NOTES

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4) Satisfactory spectral data were obtained for all new compounds with elementary analyses or high resolution MS. ^{1}H-NMR spectra were measured in $CDCl_3$ at 100 MHz for 11—14 and at 270 MHz for 15—22. ^{13}C-NMR spectra were run at 67.8 MHz.

5) E. Wenkert, C-J. Chang, H.P.S. Chawla, D.W. Cochran, E.W. Hagaman, J.C. King and K. Orito, J. Am. Chem. Soc., 98, 3645 (1976).

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7) The stereostructures were confirmed by analyses of ^{13}C-NMR spectra (Table).

8) Reserpine (9) was oxidized with *t*-BuOCl followed by treatment with HCl in refluxing MeOH to give 3-dehydroreserpine chloride [91%; mp 184°C)], which was treated with aq. KOH/MeOH to give 3,14-dehydroreserpine (15) [84%; ^{1}H-NMR δ: 4.61(1H,s,H-14)].

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