NOVEL ZINC MEDIATED INDOLE RING OPENING OF ISORESERPINE

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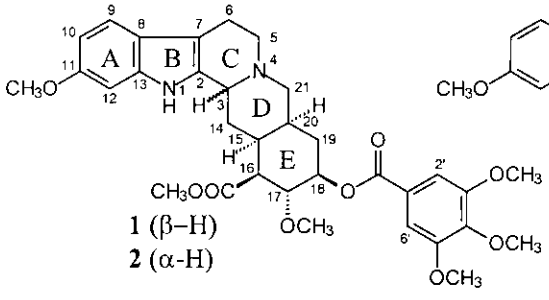
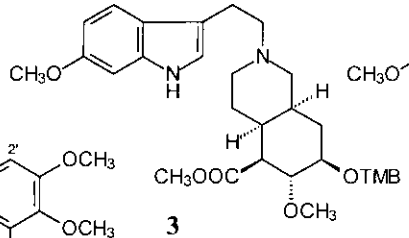
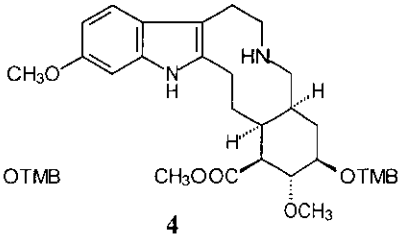
Abstract - Reaction of reserpine (**1**) with Zn/TFA resulted in isoreserpine (**2**), dihydro compound (**7**), and amino compound (**8**) *via* initial epimerization at C-3. The latter two compounds constitute a novelty in indole alkaloid chemistry: the dihydro compound (**7**) possesses unusual H-2/H-7 *cis* and H-2/H-3 *trans* relationships, whereas the amino compound (**8**) displays a novel zinc mediated indole ring scission.

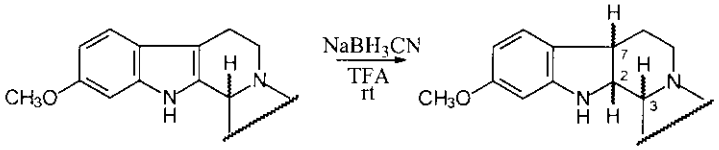
In addition to its significant pharmacology, the chemistry of the indole alkaloid reserpine (**1**)[1] has been intensively studied over the years.[2] Under reductive conditions reserpine has been reported to yield hydrogenated products, and even ring cleavages have been observed. In connection with their mechanistic studies on the acid-catalysed epimerization of **1** into its C-3 epimer isoreserpine (**2**), both Gaskell and Joule[3] and Cook and co-workers[4] trapped intermediates by utilizing zinc in refluxing acetic acid. Two products were obtained: a C-2–C-3 bond cleavage compound (**3**, minor product) and a C-3–N-4 bond cleavage compound (**4**, major product).







On the other hand, when Royer *et al.*[5] subjected reserpine (**1**) or isoreserpine (**2**) to trifluoroacetic acid (TFA) and $NaBH_3CN$ at room temperature, the corresponding 2,7-dihydro compounds (**5**) and (**6**) were obtained, respectively (Scheme 1).



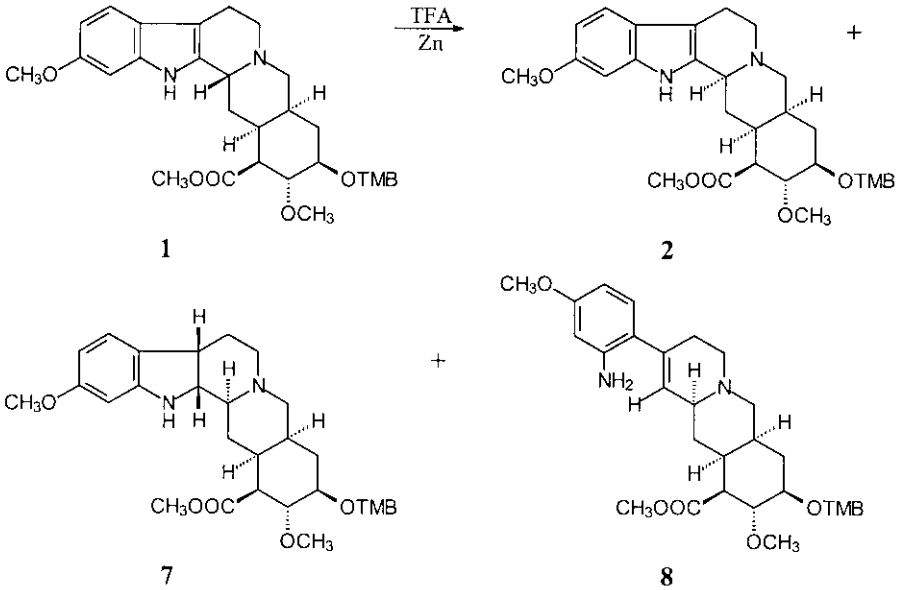
1 (H-3β) **5** (H-2β, H-3β, H-7β)
2 (H-3α) **6** (H-2α, H-3α, H-7α)

Scheme 1

We have recently utilized TFA in epimerizing indolo[2,3-*a*]quinolizidine derivatives.[6] Continuing our studies on the mechanistic aspects of the process we reasoned that reduction of reserpine (**1**) carried out with a strong acid under vigorous conditions could provide new products.

RESULTS AND DISCUSSION

When reserpine (**1**) was refluxed in TFA with zinc for 4 h, a mixture of isoreserpine (**2**) (10%), dihydro compound (**7**) (35%), and a third product (**8**) (15%) was obtained (Scheme 2). Inspection of the NMR spectra of the compounds revealed immediately that **7** and **8** were C-3 isomers of reserpine (**1**), possessing a C/D *trans* ring junction corresponding to isoreserpine (**2**). To verify that isoreserpine (**2**) is, in fact, the species where the reduction takes place, it was subjected to the same conditions as reserpine (**1**). The product composition that was obtained was the same.[7] This is a reasonable result in the light of our observation that reserpine rapidly epimerizes to isoreserpine (**2**) in refluxing TFA.[8]

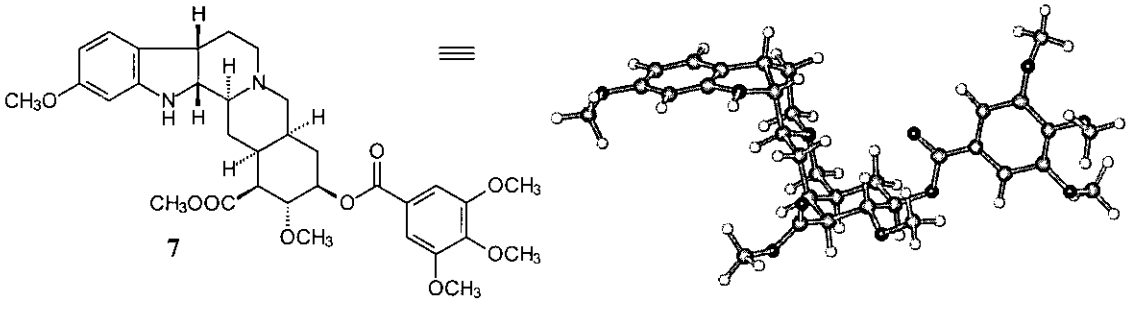


1 **2**

7 **8**

Scheme 2

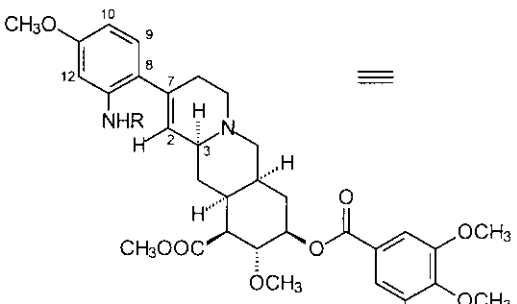
The structure elucidation of 2,7-dihydroisoreserpine (**7**) relied on *J* couplings, DQF-COSY and NOE experiments. The NMR studies were commenced with use of $CDCl_3$ as solvent, but peak overlap in the crucial areas (H-2 and H-7) persuaded a change to benzene-d_6. This reduced the peak overlap significantly. With the help of the DQF-COSY spectrum, the ddd system at δ 1.49 ppm was unequivocally assigned to H-14β. Such a coupling system is only possible in the iso-series, which means that H-3 must be α. Further evidence was obtained from the IR spectrum, which displayed strong Wenkert-Bohlmann bands. Through comparison of the obtained dihydro compound with the Royer *et al.* compound (**6**), one of the four possible stereoisomers could be eliminated. Several indications in the NMR data led us to structure (**7**). The coupling system of H-2 (δ 3.07, dd, J = 8 and 8 Hz) is in accordance with structure (**7**). In compound (**6**), where H-7 is α, the coupling system is a doublet of triplets,[5] whereas in our compound (**7**) this signal is a broad triplet, which corresponds well to β–H. This was confirmed by an NOE experiment. Irradiation at H-2 resulted in NOEs at H-7 (δ 3.2), H-14α (δ 1.56), H-14β (δ 1.49), and H-3 (δ1.39). The surprising feature was the clearly visible NOE at H-3. This can be explained by the torsion angle between H-2 and H-3, which is not 180° but closer to 160°. In addition, irradiation at H-9 resulted in a strong NOE at H-6α. Only the stereochemistry depicted in structure (**7**) permits H-9 and H-6α to come close enough in space. The ^1H NMR data of dihydro compound (**7**) are presented in Table 1.



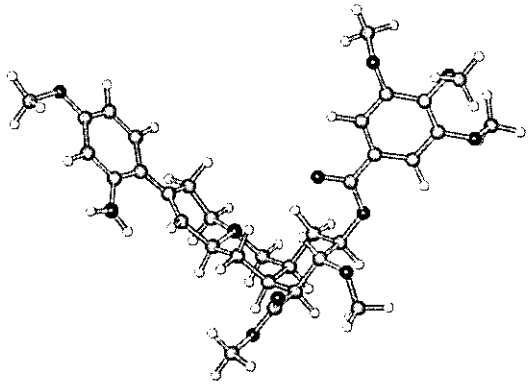
The structure elucidation of product (**8**) relied on NMR and MS spectrometries. The MS spectrum showed that the molecular weight had increased by two units relative to reserpine (**1**). This would correspond to a dihydro compound, and indeed the proton NMR spectra of **7** and **8** had many features in common. However, the proton spectrum of **8** displayed an interesting broad singlet at δ 5.49 ppm, which suggested a double bond proton. Verification was obtained from the carbon spectrum, which showed, in comparison with the spectrum of compound (**7**), two additional signals in the aromatic region and, correspondingly, two signals were missing in the aliphatic region. The next task was to locate the double bond. With the help of DQF-COSY we established that the A, D, and E rings were intact. Thus the double bond had to be located in ring C. From the COSY spectrum we were able to establish that protons H-5

and H-6 as well as H-3 were present, and the double bond must be present between C-2 and C-7. To obtain an increase in the molecular weight of two units, the bond between N-1 and C-2 had to be cleaved. On this basis we concluded that the amino compound has the structure shown below.

Acylation of compound (**8**) in pyridine and acetic anhydride provided chemical proof for the indole ring opening, as anilide (**9**) was obtained in 93% yield. The ^{1}H NMR spectrum of **9** (Table 1) displayed the characteristic shifts for an anilide NH (δ 7.51 br s) and for an acyl methyl group (δ 2.17 s).



8 (R=H)
9 (R=Ac)



8

As in the case of the dihydro compounds (**5**) and (**6**), the new dihydro derivative (**7**) is formed by protonation at C-7 of isoreserpine (**2**), which is obtained by initial epimerization of reserpine (**1**), followed by zinc reduction of the resulting iminium species. Compound (**7**) with its H-2/H-7 *cis* and H-2/H-3 *trans* relationships constitutes a novelty since the reduction of the corresponding iminium derivatives has been reported to give usually dihydro products possessing the same stereochemistry as in compounds (**5**) and (**6**) (H-2, H-3 and H-7 all *cis*).[5,9] Under these conditions, protonation of compound (**2**) at C-7 has to produce an iminium intermediate where H-3 and H-7 are *trans*. The use of zinc as reducing agent is probably responsible for the H-2/H-7 *cis* stereochemistry in compound (**7**).[10]

The new amino compound (**8**) possesses a 2-vinylaniline moiety. At first glance one could expect that compound (**8**) is formed from compound (**7**) as a result of N_a protonation and subsequent proton cleavage from C-7. This was easily confirmed not to be the case, as treatment of dihydro compound (**7**) with Zn/TFA yielded back only starting material. Zinc in acid solution is known to cleave C–N bonds in certain cases, the classic example of which involves folic acid.[11] The general reaction backwards, *i.e.* formation of indoles from 2-vinylanilines, also is well known.[12] Apparently, then, the formation of compound (**8**) involves, to the best of our knowledge, a novel zinc mediated ring scission in indole derivatives.

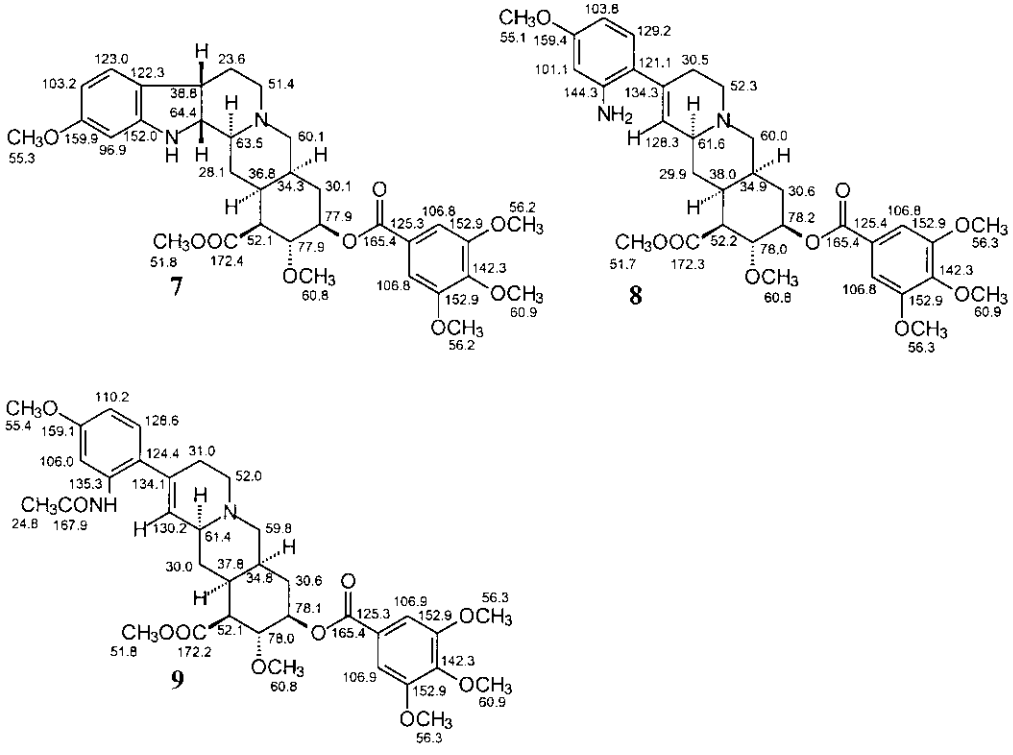
Table 1. ^{1}H NMR data of compounds (**7**), (**8**), and (**9**) (methyl shifts are omitted).

Proton	7*	8	9
H-2	3.07 dd $J_{2,3}$ = 8; $J_{2,7}$ = 8	5.49 br s	5.46 br s
H-3	1.39 ddd $J_{2,3}$ = 8; $J_{3,14\alpha}$ = 3; $J_{3,14\beta}$ = 12	2.54 br dd $J_{2,3} \approx 0$; $J_{3,14\alpha}$ = 2; $J_{3,14\beta}$ = 13	2.57 br dd $J_{2,3} \approx 0$; $J_{3,14\alpha}$ = 2; $J_{3,14\beta}$ = 13
H-5α	1.9 m	2.39 ddd $J_{5\alpha,5\beta}$ = 11; $J_{5\alpha,6\alpha}$ = 4; $J_{5\alpha,6\beta}$ = 11	2.40 ddd $J_{5\alpha,5\beta}$ = 11; $J_{5\alpha,6\alpha}$ = 4; $J_{5\alpha,6\beta}$ = 11
H-5β	1.9 m	2.79 ddd $J_{5\alpha,5\beta}$ = 11; $J_{5\beta,6\alpha}$ = 5.5; $J_{5\beta,6\beta} \approx$ 1	2.81 ddd $J_{5\alpha,5\beta}$ = 11; $J_{5\beta,6\alpha}$ = 5.5; $J_{5\beta,6\beta} \approx$ 1
H-6α	2.1 m	2.6 m	2.6 m
H-6β	1.8 m	2.2 m	2.1 m
H-7	3.2 m	-	-
H-9	6.81 dd $J_{7,9}$ = 1; $J_{9,10}$ = 8	6.91 d $J_{9,10}$ = 8.5	7.01 d $J_{9,10}$ = 8.5
H-10	6.39 dd $J_{9,10}$ = 8; $J_{10,12}$ = 2.5	6.30 dd $J_{9,10}$ = 8.5; $J_{10,12}$ = 2.5	6.63 dd $J_{9,10}$ = 8.5; $J_{10,12}$ = 2
H-12	5.98 d $J_{10,12}$ = 2.5	6.26 d $J_{10,12}$ = 2.5	7.91 d $J_{10,12}$ = 2
H-14α	1.56 ddd $J_{3,14\alpha}$ = 3; $J_{14\alpha,14\beta}$ = 13; $J_{14\alpha,15}$ = 5	1.33 ddd $J_{3,14\alpha}$ = 2; $J_{14\alpha,14\beta}$ = 13; $J_{14\alpha,15}$ = 3	1.37 ddd $J_{3,14\alpha}$ = 2; $J_{14\alpha,14\beta}$ = 13; $J_{14\alpha,15}$ = 3
H-14β	1.49 ddd $J_{3,14\beta}$ = 12; $J_{14\alpha,14\beta}$ = 13; $J_{14\beta,15}$ = 12	1.63 ddd $J_{3,14\beta}$ = 13; $J_{14\alpha,14\beta}$ = 13; $J_{14\beta,15}$ = 12	1.61 ddd $J_{3,14\beta}$ = 13; $J_{14\alpha,14\beta}$ = 13; $J_{14\beta,15}$ = 12
H-15	1.74 dddd $J_{14\alpha,15}$ = 5; $J_{14\beta,15}$ = 12; $J_{15,16}$ = 4; $J_{15,20}$ = 5	2.3 m	2.3 m
H-16	2.76 dd $J_{15,16}$ = 4; $J_{16,17}$ = 11	2.75 dd $J_{15,16}$ = 5; $J_{16,17}$ = 11	2.76 dd $J_{15,16}$ = 5; $J_{16,17}$ = 11
H-17	4.17 dd $J_{16,17}$ = 11; $J_{17,18}$ = 9.5	3.85 dd $J_{16,17}$ = 11; $J_{17,18}$ = 9.5	3.83 dd $J_{16,17}$ = 11; $J_{17,18}$ = 9.5
H-18	5.41 ddd $J_{17,18}$ = 9.5; $J_{18,19\alpha}$ = 5; $J_{18,19\beta}$ = 12	5.05 ddd $J_{17,18}$ = 9.5; $J_{18,19\alpha}$ = 5; $J_{18,19\beta}$ = 11	5.04 ddd $J_{17,18}$ = 9.5; $J_{18,19\alpha}$ = 5; $J_{18,19\beta}$ = 11
H-19α	1.97 ddd $J_{18,19\alpha}$ = 5; $J_{19\alpha,19\beta}$ = 13; $J_{19\alpha,20}$ = 4	1.99 ddd $J_{18,19\alpha}$ = 5; $J_{19\alpha,19\beta}$ = 12.5; $J_{19\alpha,20}$ = 4	2.03 ddd $J_{18,19\alpha}$ = 5; $J_{19\alpha,19\beta}$ = 12.5; $J_{19\alpha,20}$ = 4
H-19β	2.40 ddd $J_{18,19\beta}$ = 12; $J_{19\alpha,19\beta}$ = 13; $J_{19\beta,20}$ = 12	2.27 ddd $J_{18,19\beta}$ = 11.5; $J_{19\alpha,19\beta}$ = 12.5; $J_{19\beta,20}$ = 11.5	2.26 ddd $J_{18,19\beta}$ = 11; $J_{19\alpha,19\beta}$ = 12.5; $J_{19\beta,20}$ = 11
H-20	1.23 br d $J_{15,20}$ = 5; $J_{19\alpha,20}$ = 4; $J_{19\beta,20}$ = 12; $J_{20,21\alpha}$ = 3; $J_{20,21\beta}$ =2	2.0 m	2.1 m
H-21α	1.63 dd $J_{20,21\alpha}$ = 3; $J_{21\alpha,21\beta}$ = 11.5	2.44 dd $J_{20,21\alpha}$ = 3; $J_{21\alpha,21\beta}$ = 11	2.48 dd $J_{20,21\alpha}$ = 3; $J_{21\alpha,21\beta}$ = 11
H-21β	2.17 dd $J_{20,21\beta}$ = 2; $J_{21\alpha,21\beta}$ = 11.5	2.72 dd $J_{20,21\beta} \approx$ 1; $J_{21\alpha,21\beta}$ = 11	2.74 dd $J_{20,21\beta} \approx$ 1; $J_{21\alpha,21\beta}$ = 11
H-2' and H-6'	7.63 s	7.33 s	7.32 s
-NHCOCH_3	-	-	2.17 s
-NHCOCH$_3$	-	-	7.51 br s

* : [D_6]benzene used as solvent

CONCLUSIONS

A new dihydro derivative (**7**) was obtained as major product in the Zn/TFA reduction of both reserpine (**1**) and isoreserpine (**2**). Reduction of the N_a iminium species usually yields a H-2/H-3/H-7 all *cis* product (*vide supra*), but compound (**7**) possesses a H-2/H-7 *cis* and H-2/H-3 *trans* stereochemistry. Under the same conditions an amino compound (**8**), presenting a novel N_a–C-2 bond scission, was formed. Inspection of the generality of the new indole ring opening observed here with isoreserpine has provided the basis for further investigations in our laboratory.



Scheme 3

EXPERIMENTAL

Except where otherwise stated, all reactions were carried out under argon. Alkaline work-up comprised addition of saturated aq $NaHCO_3$, extraction with CH_2Cl_2 (3x), drying of the combined organic layers with Na_2SO_4 and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, KBr) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (399.958 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100.578 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ or benzene-d_6 used as solvent. Coupling constants (*J*) are given in Hz. Signal

assignments are based on standard APT, DEPT, DQF-COSY, NOE, HETCOR, and long-range HETCOR experiments. For the ^{13}C NMR data of compounds (**7**)-(**9**), see Scheme 3. EI and HR MS spectra (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography.

Reduction of Reserpine (1) with Zinc. Reserpine (**1**) (583.6 mg, 0.96 mmol) was dissolved in TFA (7 mL). Zinc (1.30 g, 19.9 mmol) was added to the solution, which was then refluxed for 4 h. TFA was evaporated and the residue was made alkaline with saturated aq $NaHCO_3$. Then CH_2Cl_2 was added and the solution was filtered through Celite. The filter cake was washed with CH_2Cl_2 and the organic phase was separated. The water phase was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 99.4:0.6-97.5-2.5) and preparative TLC (acetone:CH_2Cl_2, 50:50) to yield 207 mg (35%) of dihydro isoreserpine (**7**), 86 mg (15%) of amorphous (**8**), and 58 mg (10%) of isoreserpine (**2**).[13]

Dihydro compound (**7**): mp. 201-203°C (MeOH); IR: 2820-2750 (Wenkert-Bohlmann bands), 1740 (C=O), 1710 (C=O); MS: 610 (M^+, 27), 463 (17), 450 (100), 252 (71), 212 (32), 195 (63); HR-MS calcd for $C_{33}H_{42}N_2O_9$: 610.2890, found: 610.2868; Anal. Calcd for $C_{33}H_{42}N_2O_9$: C 64.90, H 6.93, N 4.59, found: C 64.80, H 7.14, N 4.18.

Amino compound (**8**): IR: 2820-2750 (Wenkert-Bohlmann bands), 1720 (C=O), 1700 (C=O); MS: 610 (M^+, 58), 450 (14), 399 (100), 383 (23), 367 (13), 256 (17), 195 (43); HR-MS calcd for $C_{33}H_{42}N_2O_9$: 610.2890, found: 610.2897.

Acylation of Amino Compound (8). Amino compound (**8**) (24.9 mg, 0.04 mmol) was dissolved in acetic anhydride (0.5 mL, 5.3 mmol) and pyridine (0.5 mL) and the mixture was stirred at rt for 15.5 h. After evaporation alkaline work-up was performed. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 99:1) to give 24.7 mg (93%) of amorphous (**9**); IR: 2820-2750 (Wenkert-Bohlmann bands), 1750-1700 3x(C=O); MS: 652 (M^+, 93), 637 (16), 609 (30), 594 (38), 441 (46), 425 (37) 409 (31), 195 (100); HR-MS calcd for $C_{35}H_{44}N_2O_{10}$: 652.2996, found: 652.3007.

REFERENCES AND NOTES

1. Biogenetic numbering: J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
2. E. Schlittler, "*Rauwolfia* Alkaloids with Special Reference to the Chemistry of Reserpine", in *The Alkaloids* Vol. 8, ed. by R. H. F. Manske, Academic Press, New York, 1965, pp. 287-334.
3. A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.

4. L.-H. Zhang, A. K. Gupta, and J. M. Cook, *J. Org. Chem.*, 1989, **54**, 4708.
5. D. Royer, M. Doé de Maindreville, J.-Y. Laronze, J. Lévy, and R. Wen, *Tetrahedron*, 1996, **52**, 9069.
6. M. Lounasmaa, M. Berner, and A. Tolvanen, *Heterocycles*, 1999, **50**, 243.
7. The reaction mixture obtained from isoreserpine (**2**) displayed slightly different ratios than that of reserpine (**1**).
8. M. Lounasmaa, M. Berner, A. Tolvanen, and R. Jokela, *Heterocycles*, in press.
9. G. W. Gribble, J. L. Johnson, and M. G. Saulnier, *Heterocycles*, 1981, **16**, 2109.
10. L. J. Dolby and G. W. Gribble, *J. Heterocycl. Chem.*, 1966, **3**, 124.
11. G. P. Lewis and P. B. Rowe, *Anal. Biochem.*, 1979, **93**, 91.
12. R. J. Sundberg, Indoles, in *Best Synthetic Methods*, eds. A. R. Katritzky, O. Meth-Cohn, C. W. Rees, Academic Press, New York, 1996.
13. S. F. Martin, H. Rüeger, S. A. Williamson, and S. J. Grzejszczak, *J. Am. Chem. Soc.*, 1987, **109**, 6124.

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