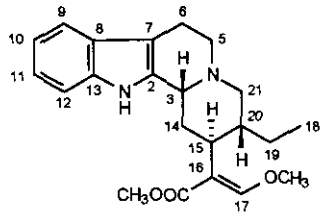
PREPARATION OF (±)-HIRSUTINE AND (±)-3-ISOCORYNANTHEIDINE

Mauri Lounasmaa*, Reija Jokela, Christiane Laine, and Pirjo Hanhinen

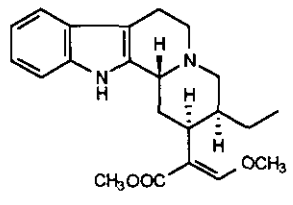
Laboratory for Organic and Bioorganic Chemistry, Technical University of Helsinki, FIN-02150 Espoo, Finland

Abstract - Preparation of indole alkaloids (±)-hirsutine (**1**) and (±)-3-isocorynantheidine (**2**) is described.

Hirsutine (**1**), a tetracyclic indole alkaloid, was first isolated by Shellard *et al.*[1] from the Asian plant, *Mitragyna hirsuta* Havil. Its 20-epimer, 3-isocorynantheidine (**2**), was also first isolated by Shellard *et al.*,[2] but from another Asian plant, *Mitragyna speciosa* Korth. Later, the presence of both compounds was demonstrated in several *Mitragyna* and *Uncaria* species (Rubiaceae).[3-6] Various syntheses (total or partial) of hirsutine (**1**) and 3-isocorynantheidine (**2**) have been presented,[7-12] but they are generally relatively long and tedious. We recently described a short synthesis of hirsutine (**1**).[13]



1



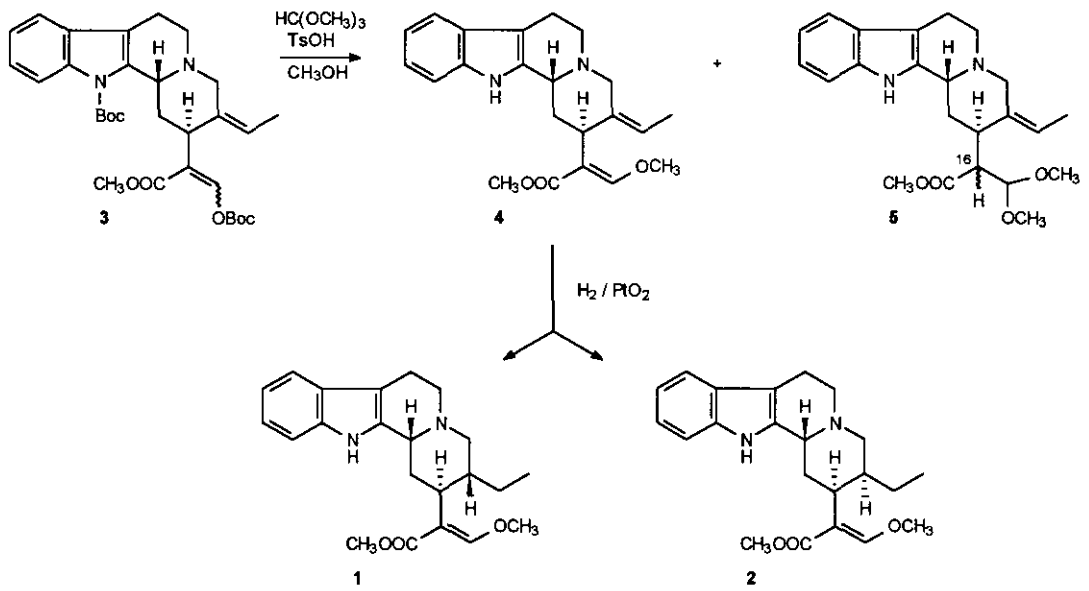
2

Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

We have now developed an easy alternative route to (±)-hirsutine (**1**), as well as a route to (±)-3-isocorynantheidine (**2**).

RESULTS AND DISCUSSION

Treatment of our recently described and easily accessible (±)-N_a,*O*-di-Boc-3-epi-*Z*-geissoschizine [=(±)-N_a,*O*-di-Boc-15-epi-*Z*-geissoschizine][14] (**3**) with trimethyl orthoformate and TsOH in MeOH gave a mixture of (±)-3-epi-*Z*-geissoschizine methyl ether (**4**)[15] and (±)-3-epi-*Z*-geissoschizine dimethylacetal (**5**) (as a mixture of C-16 epimers), which was easily fractionated. Catalytic hydrogenation (PtO_2) of compound (**4**) led to two dihydro derivatives, (±)-hirsutine (**1**) and (±)-3-isocorynantheidine (**2**) (Scheme 1).



Scheme 1. Preparation of (±)-hirsutine (**1**) and (±)-3-isocorynantheidine (**2**) from (±)-N_a,*O*-di-Boc-3-epi-*Z*-geissoschizine (**3**).

The ^{13}C-NMR data (Figure 1) are in good agreement with the proposed structures.[13,14,16]

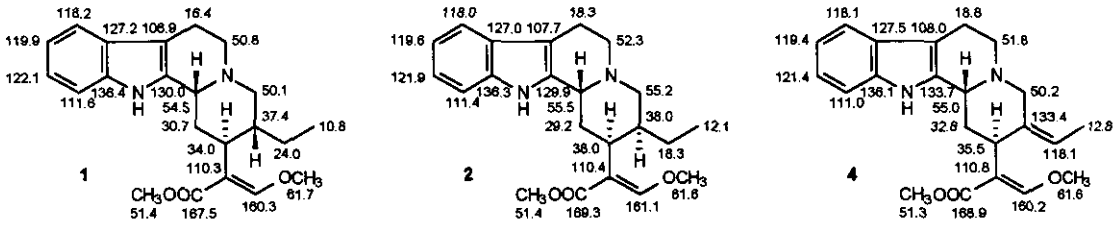


Figure 1. ^{13}C-NMR data of compounds (**1**, **2**, and **4**).

CONCLUSIONS

A new easy route is now available for the preparation of (±)-hirsutine (**1**) and (±)-3-isocorynantheidine (**2**). Complete ^{1}H- and ^{13}C-NMR data of compounds (**1**) and (**2**) are presented for the first time. For earlier fragmentary ^{1}H-NMR data, see Refs. 17-19.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 spectrophotometer in $CHCl_3$. IR absorption bands are given in reciprocal centimetres (cm^{-1}). ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^{1}H-NMR) and 50.289 MHz (^{13}C-NMR) or a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-NMR) and 100.577 MHz (^{13}C-NMR). Chemical shifts are given in ppm by reference to TMS (^{1}H-NMR; δ_H=0.0 ppm) and $CDCl_3$ (^{13}C-NMR; δ_C=77.0 ppm). Abbreviations s, d, t, q, m and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. For the ^{13}C-NMR data, see Figure 1. Mass spectrometry (EIMS and HRMS) was done with a JEOL DX 303/DA 5000 instrument.

Preparation of (±)-3-epi-*Z*-geissoschizine methyl ether (4) and (±)-3-epi-*Z*-geissoschizine dimethylacetal (5). (±)-N_a,*O*-Di-Boc-3-epi-*Z*-geissoschizine[14] (**3**) (60 mg, 0.11 mmol) was dissolved in 3 mL of CH_3OH. After addition of $CH(OCH_3)_3$ (0.23 mL, 2.10 mmol, 19f equiv.) and TsOH (50 mg) the solvent was slowly evaporated under stirring during 90 min (oil bath, 75°C). The residue was dissolved in CH_2Cl_2, neutralized with 10% Na_2CO_3, washed with H_2O, dried with Na_2SO_4, and filtered. After evaporation, the crude mixture was purified and fractionated with PLC (silica gel, CH_2Cl_2/CH_3OH, 90/10) to yield compounds (**4**) and (**5**).

(±)-3-Epi-*Z*-geissoschizine methyl ether (4). Yield 10.0 mg (25%). Amorphous. IR: 3350 (m, N-H), 1700 (s, C=O), 1640 (m, -C=C-). ^{1}H-NMR: 1.63 (3H, d, J=7 Hz, H-18), 2.02 (1H, ddd, J_1=14 Hz, J_2=J_3=6 Hz, H-14β), 2.65 (1H, ddd, J_1=14 Hz, J_2=10 Hz, J_3=5 Hz, H-14α), 2.70 (1H, br d, J=13 Hz, H-6α), 3.01 (1H, ddd, J_1=12 Hz, J_2=11 Hz, J_3=4 Hz, H-5α), 3.10 (1H, m, H-6β), 3.30 (1H, ddd, J_1=12 Hz, J_2=5 Hz, J_3=1 Hz, H-5β), 3.45 (2H, def., H-21α, H-21β), 3.52 (1H, m, H-15), 3.68 (3H, s, -$COOCH_3$), 3.79 (3H, s, -C=C-OCH_3), 4.16 (1H, br s, H-3), 5.18 (1H, q, J=7 Hz, H-19), 7.09 (1H, t, J=7.5 Hz, H-10), 7.15 (1H, t, J=7.5 Hz, H-11), 7.33 (1H, d, J=7.5 Hz, H-12), 7.42 (1H, s, H-17), 7.48 (1H, d, J=7.5 Hz, H-9), 7.97 (1H, br s, NH). For the ^{13}C-NMR data, see Figure 1. MS: 366 (M^+, 100%), 365, 351, 335, 249, 237, 223, 184, 170, 169, 156. HRMS: Calcd for $C_{22}H_{26}N_2O_3$: 366.1943. Found: 366.1930. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.84; H, 6.99; N, 7.38.

(±)-3-Epi-*Z*-geissoschizine dimethylacetal (5) (mixture of C-16 epimers). Yield 22.0 mg (50%). Amorphous. For the analytical data, see Ref. 16.

Preparation of (±)-hirsutine (1) and (±)-3-isocorynantheidine (2). (±)-3-Epi-*Z*-geissoschizine methyl ether (**4**) (11.0 mg, 0.030 mmol) was hydrogenated (PtO_2, 11 mg) in CH_3OH (5 ml) for 1 h. After normal work-up, the crude mixture was purified and fractionated by PLC (silica gel, CH_2Cl_2/CH_3OH; 90/10) to yield compounds (**1**) and (**2**).

(±)-Hirsutine (1). Yield 4.0 mg (36%). mp 128-130°C (EtOH/Et_2O). IR: 3400 (m, N-H), 1700 (s, C=O), 1640 (m, -C=C-). ^{1}H-NMR: 0.75 (3H, def. t, H-18), 3.70 (3H, s, -$COOCH_3$), 3.79 (3H, s, -C=C-OCH_3), 4.77 (1H, br s, H-3), 7.15 (1H, t, J=8 Hz, H-10), 7.19 (1H, t, J=8 Hz, H-11), 7.35 (1H, s, H-17), 7.44 (1H, d, J=8 Hz, H-12), 7.51 (1H, d, J=8 Hz, H-9), 8.32 (1H, br s, NH). For the ^{13}C-NMR data, see Figure 1. MS: 368 (M^+, 100%), 367, 353, 339, 337, 311, 251, 225, 197, 184, 170, 169, 156. HRMS: Calcd for $C_{22}H_{28}N_2O_3$: 368.2100. Found: 368.2089.

(±)-3-Isocorynantheidine (2). Yield 4.0 mg (36%). mp 216-218°C (EtOH/Et_2O). IR: 3300 (m, N-H), 1700 (s, C=O), 1635 (m, -C=C-). ^{1}H-NMR: 0.87 (3H, t, J=7 Hz, H-18), 3.65 (3H, s, -$COOCH_3$), 3.80 (3H, s, -C=C-OCH_3), 4.51 (1H, br s, H-3), 7.11 (2H, m, H-10, H-11), 7.36 (1H, d, J=8 Hz, H-12), 7.41 (1H, s, H-17), 7.43 (2H, m, H-9, NH). For the ^{13}C-NMR data, see Figure 1. MS: 368 (M^+), 367, 353, 339, 337, 251, 239, 225, 197, 184 (100%), 170, 169, 156. HRMS: Calcd for $C_{22}H_{28}N_2O_3$: 368.2100. Found: 368.2093.

REFERENCES AND NOTES

1. E. J. Shellard, A. H. Beckett, P. Tantivatana, J. D. Phillipson, and C. M. Lee, *J. Pharm. Pharmac.*, 1966, **18**, 553. See also, E. J. Shellard, P. Tantivatana, and A. H. Beckett, *Planta Medica*, 1967, **15**, 366 and J. Haginiwa, S. Sakai, N. Aimi, E. Yamanaka, and N. Shinma, *Yakugaku Zasshi*, 1973, **93**, 448.
2. E. J. Shellard, P. J. Houghton, and M. Resha, *Planta Med.*, 1978, **34**, 253.
3. S. R. Hemingway and J. D. Phillipson, in "*Indole and Biogenetically Related Alkaloids*", ed. by J. D. Phillipson and M. H. Zenk, Academic Press, London, 1980, pp. 63-90.
4. R. T. Brown, in "*The Monoterpenoid Indole Alkaloids*", ed. by J. E. Saxton, John Wiley, New York, 1983, pp. 63-146.
5. C. Szántay, G. Blaskó, K. Honty, and G. Dörnyei, in "*The Alkaloids*", ed. by A. Brossi, Vol. 27, Orlando, Academic Press, 1986, pp. 131-268 and 407-410.
6. M. Lounasmaa and A. Tolvanen, in "*The Monoterpenoid Indole Alkaloids*", ed. by J. E. Saxton, Suppl. Vol., John Wiley, Chichester, 1994, pp. 57-159.
7. R. T. Brown and C. L. Chapple, *J. Chem. Soc., Chem. Commun.*, **1973**, 886.
8. R. T. Brown, C. L. Chapple, and A. A. Charalambides, *J. Chem. Soc., Chem. Commun.*, **1974**, 756.
9. N. Aimi, E. Yamanaka, J. Endo, S. Sakai, and J. Haginiwa, *Tetrahedron*, 1973, **29**, 2015.
10. E. Wenkert, Y. D. Vankar, and J. S. Yadav, *J. Am. Chem. Soc.*, 1980, **102**, 7971.
11. R. T. Brown, M. F. Jones, and M. Wingfield, *J. Chem. Soc., Chem. Commun.*, **1984**, 847.
12. D. Gomez-Pardo, D. Desmaële, and J. d´Angelo, *Tetrahedron Lett.*, 1992, **33**, 6633.
13. M. Lounasmaa, J. Miettinen, P. Hanhinen, and R. Jokela, *Tetrahedron Lett.*, 1997, **38**, 1455.
14. B. Tirkkonen, J. Miettinen, J. Salo, R. Jokela, and M. Lounasmaa, *Tetrahedron*, 1994, **50**, 3537. See also, M. Lounasmaa, R. Jokela, U. Anttila, P. Hanhinen, and C. Laine, *Tetrahedron*, 1996, **52**, 6803 (Note 11).

15. The *trans* relationship between the methoxycarbonyl and methoxyl groups in the methyl β-methoxyacrylyl moiety of compound (**4**) was confirmed by a comparison of the chemical shift value found for C-17-H (δ 7.42; *vide supra*) with the calculated values (*cis* δ 6.80; *trans* δ 7.37).[20,21]
16. M. Lounasmaa, R. Jokela, M. Bäck, P. Hanhinen, and C. Laine, *Tetrahedron*, 1995, **51**, 11891.
17. W. F. Trager, C. M. Lee, J. D. Phillipson, and A. H. Beckett, *Tetrahedron*, 1967, **23**, 1043.
18. A. H. Beckett, D. Dwuma-Badu, and R. E. Haddock, *Tetrahedron*, 1969, **25**, 5961.
19. S. Sakai and N. Shinma, *Chem. Pharm. Bull.*, 1978, **26**, 2596.
20. M. Hesse, H. Meier, and B. Zeeh, "*Spektroskopische Methoden in der organischen Chemie*", 3rd Ed., Georg Thieme Verlag, Stuttgart, 1987, p. 115.
21. M. Lounasmaa, R. Jokela, C. Laine, and P. Hanhinen, *Tetrahedron Lett.*, 1995, **36**, 8687.

Received, 8th January, 1998