

STRUCTURE AND SYNTHESIS OF TWO NEW TYPES OF OXINDOLE ALKALOIDS FOUND FROM UNCARIA SALACCENSIS

Dhavadee PONGLUX,^a Sumphan WONGSERIPIPATANA,^a Norio AIMI,^b Masashi NISHIMURA,^b Midori ISHIKAWA,^b Hiroyuki SADA,^b Joju HAGINIWA,^b and Shin-ichiro SAKAI^b
 Faculty of Pharmaceutical Sciences, Chulalongkorn University,^a Bangkok 10500, Thailand and Faculty of Pharmaceutical Sciences, Chiba University,^b 1-33 Yayoi-cho, Chiba 260, Japan

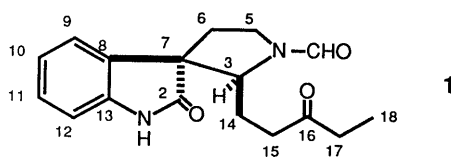
Two new types of oxindole alkaloids, salacin and 3-oxo-7-hydroxy-3,7-secorhynchophylline, have been isolated from the Thai medicinal plant Uncaria salaccensis. Their structures and syntheses are described.

KEYWORDS Uncaria salaccensis; Rubiaceae; oxindole; indole alkaloid; C-ring seco; D-ring seco

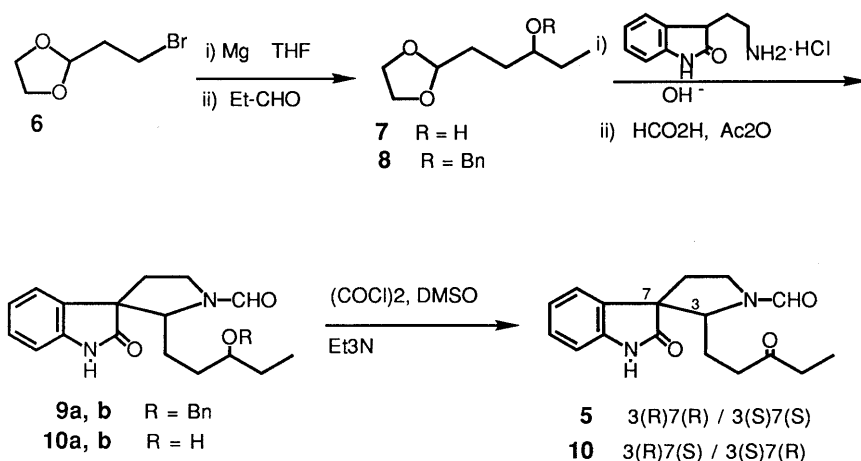
From the leaves of Uncaria salaccensis (U. attenuata) seven indole alkaloids have been isolated.^{1,2)} One member, 14 α -hydroxyrauniticine was first reported as 14 β -hydroxy-3-isorauniticine¹⁾ but later, through the aid of partial synthesis from rauniticine, the structure was revised to the present one.³⁾ In this paper we report our study on the constituents of the stem bark and hooks of the same plant.

The methanol extract was submitted to a column of DIAION HP-20 without using the conventional acid-base pretreatment. The fractions eluted with H₂O - MeOH (20% - 80%) were then further purified with silicagel columns (open column, flash column, and HPLC). Two new oxindoles, salacin (1) and compound A (2), were isolated along with the three known oxindole alkaloids rhynchophylline (3), isorhynchophylline (4) and corynoxine.

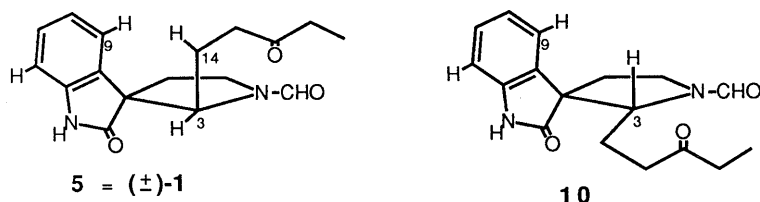
Salacin (1),⁴ C₁₇H₂₀N₂O₃, showed a typical oxindole UV spectrum. Mass and ¹H-NMR spectra indicated the structure shown below. The relative stereochemistry of salacin (1) was elucidated with NOE spectroscopy. The signal intensities of H-6 and H-14 increased on irradiation at H-9, while no NOE was observed between H-9 and H-3. The stereochemical outcome obtained here was further confirmed comparing of NOE result with that of the stereoisomeric synthetic compound.



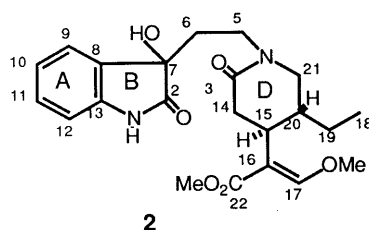
Laboratory synthesis of ($\pm$)-salacin (5) was carried out as follows. Reaction of propionaldehyde with the Grignard reagent prepared from bromoacetal (6) gave the secondary alcohol (7). Benzylation, condensation with oxytryptamine, and formylation of the resulting secondary amine gave two diastereomeric oxindoles (9a) and (9b). Removal of the protective group followed by Swern oxidation afforded two ketones, 5 and 10.



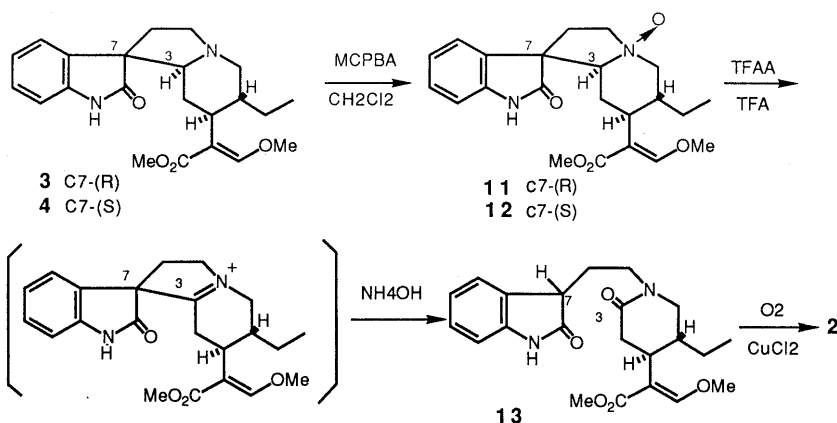
Compound (5) was entirely identical to the naturally occurring salacin (1) except for the optical properties. The other compound (10) was shown to be the stereoisomer by an NOE experiment. In contrast to (5), no NOE was observed between H-9 and H-14. To the contrary, the same effect was observed between H-3 and H-9. These findings strongly supported the deduced stereochemistry of salacin (1).



The second natural product (2)⁵, C₂₂H₂₈N₂O₆, was obtained as an amorphous powder. The UV spectrum indicated that 2 had a β-alkoxyacrylic ester moiety in addition to the oxindole chromophore. The structure was clarified by means of ¹H- and ¹³C-NMR as shown below. The ¹³C-NMR peaks with particular significance were singlets at δ 75.3 (C-7) and 170.8 (C-3). The 15_α,20_β stereochemistry was clarified with the ¹³C-NMR spectrum which was quite consistent with the model compounds.⁵ Compound A (2) was thus shown to be 3-oxo-7-hydroxy-3,7-secorhynchophylline.



The construction of this molecule was quite new and we carried out a laboratory synthesis starting from natural compounds with known absolute configuration. Rhynchophylline (3) was oxidized with MCPBA and the resulting N-oxide (11) was treated with trifluoroacetic anhydride under modified Polonovski condition. Elimination took place regioselectively to C-3 and the usual work-up gave a C-seco compound (13). Subsequent CuCl₂-catalyzed oxidation afforded the desired compound (2) in 30% yield. The same intermediate and final compounds, 13 and 2, were obtained when isorhynchophylline (4) was used as the starting material.



All the spectroscopic properties including 500 MHz ^1H -NMR and CD curve proved the complete identity of the synthetic material with the natural alkaloid. This proved unambiguously the stereochemistry at C-15 and C-20 and also the absolute configuration of the molecule. The result we obtained here also indicated that both the synthetic and natural compounds are the epimeric mixture at C-7. All the efforts to separate them have been unsuccessful so far.

ACKNOWLEDGMENT We thank the Ministry of Education, Science, and Culture of Japan for financial support by a Grant-in-Aid for Scientific Researches (63570982).

REFERENCES AND NOTES

- 1) D. Ponglux, T. Supavita, R. Verpoorte, and J. D. Phillipson, *Phytochem.*, **19**, 2013 (1980).
- 2) P. Tantivatana, D. Ponglux, S. Wongseripipatana, and J. D. Phillipson, *Planta Med.*, **40**, 299 (1980).
- 3) E. Yamanaka, E. Maruta, S. Kasamatsu, N. Aimi, S. Sakai, D. Ponglux, S. Wongseripipatana, T. Supavita, and J. D. Phillipson, *Chem. Pharm. Bull.*, **34**, 3713 (1986).
- 4) Amorphous powder. High resolution MS, m/z 300.1469 (Calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$; 300.1472). MS m/z ; 300(M^+ , 12%), 272(100), 215(35), and 187(16). $\text{UV}\lambda_{\text{max}}$ (MeOH) nm; 208, 250, and 282. ^1H -NMR (500MHz, CDCl_3)(values for major rotamer signals) δ ; 0.97(3H, t, $J=7.3\text{Hz}$, H-18), 1.67(2H, m, H-14, H-15), 2.11(1H, dd, $J=14.2, 8.3\text{Hz}$, H-15), 2.13(1H, ddd, $J=13.4, 8.6, 4.6\text{Hz}$, H-6), 2.30(2H, q, $J=7.3\text{Hz}$, H-17), 2.35(2H, m, H-6, H-14), 3.68(1H, ddd, $J=12.5, 8.6, 4.1\text{Hz}$, H-5), 3.99(1H, ddd, $J=12.5, 8.4, 4.6\text{Hz}$, H-5), 4.03(1H, dd, $J=10.2, 5.0\text{Hz}$, H-3), 6.97(1H, d, $J=7.9\text{Hz}$, H-12), 7.07(1H, dd, $J=7.9, 7.3\text{Hz}$, H-10), 7.11(1H, d, $J=7.3\text{Hz}$, H-9), 7.29(1H, dd, $J=7.9, 7.9\text{Hz}$, H-11), 8.19(1H, br. s, NH), and 8.34(1H, s, N-CHO).
- 5) Amorphous powder. MS m/z ; 416(M^+ , 18%), 388(17), 268(100), 210(28), and 146(45). $\text{UV}\lambda_{\text{max}}$ (MeOH) nm; 204.6 and 240. $\text{IR}\nu_{\text{max}}$ (CHCl_3) cm^{-1} ; 3430, 1720, 1700 and 1620. ^1H -NMR (500MHz, CDCl_3) δ ; 0.84(3H, t, $J=7.4\text{Hz}$, H-18), 1.09(1H, dq, $J=14.8, 7.4\text{Hz}$, H-19), 1.46(1H, ddq, $J=14.8, 3.7, 7.4\text{Hz}$, H-19), 2.12(1H, m, H-14), 2.25(2H, m, H-15, H-20), 2.33(1H, ddd, $J=17.3, 5.9, 5.5\text{Hz}$, H-6), 2.75(1H, ddd, $J=17.3, 11.8, 6.6\text{Hz}$, H-6), 2.86(1H, dd, $J=11.3, 5.8\text{Hz}$, H-14), 2.93(1H, dd, $J=11.4, 11.4\text{Hz}$, H-21), 3.24(1H, dd, $J=11.4, 5.0\text{Hz}$, H-21), 3.39(1H, ddd, $J=13.2, 6.6, 5.9\text{Hz}$, H-5), 3.69(3H, s, OCH_3), 3.79(1H, m, H-5), 3.81(3H, s, OCH_3), 4.86(1H, br. s, OH), 6.84(1H, d, $J=7.9\text{Hz}$, H-12), 7.07(1H, dd, $J=7.9, 7.4\text{Hz}$, H-10), 7.24(1H, dd, $J=7.9, 7.9\text{Hz}$, H-11), 7.35(1H, s, H-17), 7.44(1H, d, $J=7.4\text{Hz}$, H-9), and 7.47(1H, br. s, NH). ^{13}C -NMR (67.8MHz, CDCl_3) δ ; 10.9(C-18), 23.9(C-19), 34.8(C-15), 35.8(C-14), 36.9(C-20), 42.2(C-6), 42.3(C-21), 51.1(OCH_3), 52.6(C-5), 61.9(OCH_3), 75.3(C-7), 110.1(C-16), 110.4(C-12), 122.8(C-9), 124.2(C-10), 129.5(C-11), 131.3(C-8), 140.7(C-13), 160.4(C-17), 170.8(C-3), and 180.1(C-2).
- 6) E. Wenkert, J. S. Bindra, C-J. Chaang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974).

(Received December 7, 1989)