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

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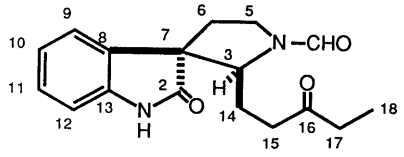
Two new types of oxindole alkaloids, salacin and 3-oxo-7-hydroxy-3,7-secorhynchophylline, have been isolated from the Thai medicinal plant Uncaria salaccensis. Their structures and syntheses are described.

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, 14α-hydroxyrauniticine was first reported as 14β-hydroxy-3-isorauniticine[1] 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.

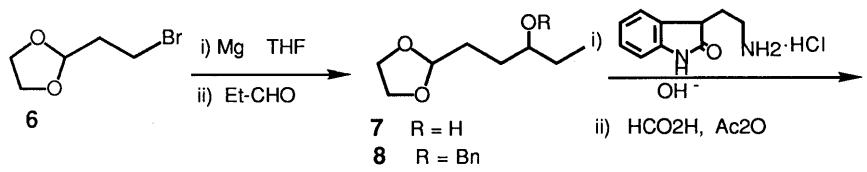
The methanol extract was submitted to a column of DIAION HP-20 without using the conventional acid-base pretreatment. The fractions eluted with H_2O - MeOH (20% - 80%) were then further purified with silicagel columns (open column, flash column, and HPLC). Two new oxindoles, salacin (**1**) and compound A (**2**), were isolated along with the three known oxindole alkaloids rhynchophylline (**3**), isorhynchophylline (**4**) and corynoxine.

Salacin (**1**),[4] $C_{17}H_{20}N_2O_3$, showed a typical oxindole UV spectrum. Mass and ^{1}H-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.



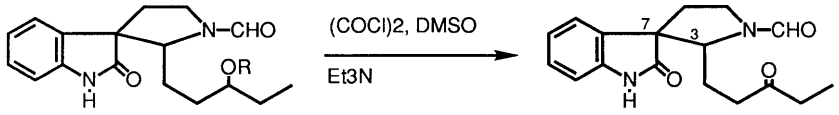
1

Laboratory synthesis of (±)-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**.



6

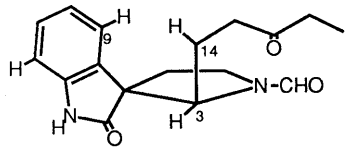
7 R = H
8 R = Bn



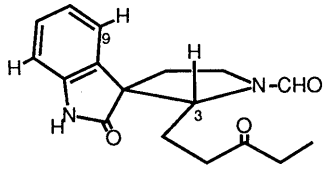
9a, b R = Bn
10a, b R = H

5 3(R)7(R) / 3(S)7(S)
10 3(R)7(S) / 3(S)7(R)

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**).

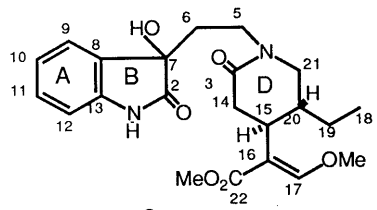


5 = (±)-**1**



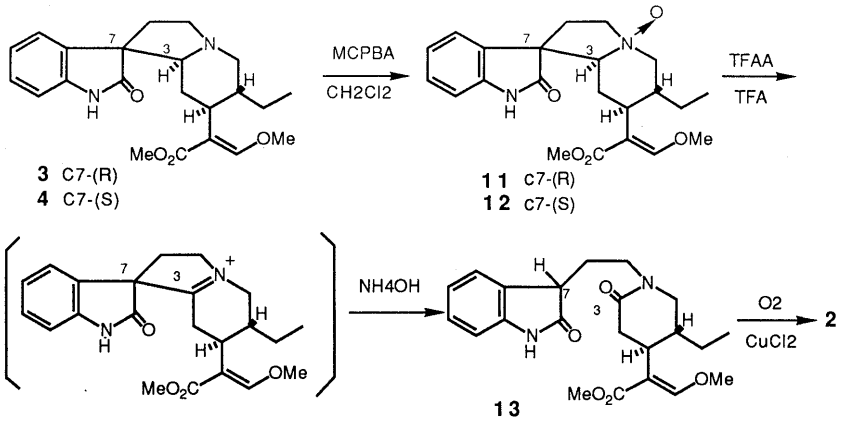
10

The second natural product (**2**)[5], $C_{22}H_{28}N_2O_6$, 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 ^{13}C-NMR as shown below. The ^{13}C-NMR peaks with particular significance were singlets at δ 75.3 (C-7) and 170.8 (C-3). The 15α,20β stereochemistry was clarified with the ^{13}C-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.



2

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 $CuCl_2$-catallized 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.



3 C7-(R)
4 C7-(S)
11 C7-(R)
12 C7-(S)
13
2

All the spectroscopic properties including 500 MHz ^{1}H-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.

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4) Amorphous powder. High resolution MS, m/z 300.1469 (Calcd. for $C_{17}H_{20}N_2O_3$; 300.1472). MS m/z; 300(M^+,12%), 272(100), 215(35), and 187(16). UVλ_{max}(MeOH) nm; 208, 250, and 282. ^{1}H-NMR (500MHz, $CDCl_3$)(values for major rotamer signals) δ ; 0.97(3H,t, J=7.3Hz, H-18), 1.67(2H,m, H-14, H-15), 2.11(1H,dd, J=14.2,8.3Hz, H-15), 2.13(1H,ddd, J=13.4, 8.6,4.6Hz, H-6), 2.30(2H,q,J=7.3Hz, H-17), 2.35(2H,m, H-6, H-14), 3.68(1H,ddd,J=12.5, 8.6,4.1Hz, H-5), 3.99(1H,ddd,J=12.5,8.4,4.6Hz, H-5), 4.03(1H,dd,J=10.2,5.0Hz, H-3), 6.97(1H,d,J=7.9Hz, H-12), 7.07(1H,dd,J=7.9,7.3Hz, H-10), 7.11(1H,d,J=7.3Hz, H-9), 7.29 (1H,dd,J=7.9,7.9Hz, 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). UV λ_{max}(MeOH) nm; 204.6 and 240. IR ν_{max}($CHCl_3$)cm^{-1}; 3430, 1720, 1700 and 1620. ^{1}H-NMR (500MHz, $CDCl_3$) δ; 0.84(3H,t,J=7.4Hz, H-18), 1.09(1H,dq, J=14.8,7.4Hz, H-19), 1.46(1H, ddq,J=14.8,3.7,7.4Hz, H-19), 2.12(1H,m,H-14), 2.25(2H,m, H-15,H-20), 2.33(1H,ddd,J= 17.3,5.9,5.5Hz, H-6), 2.75(1H,ddd,J=17.3,11.8,6.6Hz, H-6), 2.86(1H,dd,J=11.3,5.8Hz, H-14), 2.93(1H,dd,J=11.4,11.4Hz, H-21), 3.24(1H,dd,J=11.4,5.0Hz, H-21), 3.39(1H,ddd, J=13.2,6.6,5.9Hz, 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=7.9Hz, H-12), 7.07(1H,dd,J=7.9,7.4Hz, H-10), 7.24(1H,dd, J=7.9,7.9Hz, H-11), 7.35(1H,s,H-17), 7.44(1H,d,J=7.4Hz, 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).

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