Chem. Pharm. Bull. 30(11)4046—4051(1982)

Studies on Plants containing Indole Alkaloids. VIII[1] Indole Alkaloid Glycosides and Other Constituents of the Leaves of *Uncaria rhynchophylla* Miq.

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(Received May 20, 1982)

A new glycoindole alkaloid, rhynchophine, was isolated from the leaves of *Uncaria rhynchophylla* Miq. and its structure was elucidated as 6′-feruloyl vincoside lactam (IV). A partial synthesis was achieved by the use of vincoside lactam as the starting material. Five known compounds were also newly isolated from the same plant, namely, vallesiachotamine, vincoside lactam, strictosamide, hyperin and trifolin.

Keywords——indole alkaloid; glycoside; *Uncaria rhynchophylla* Miq.; Rubiaceae; ^{13}C-NMR; partial synthesis; rhynchophine; vallesiachotamine; vincoside lactam; strictosamide

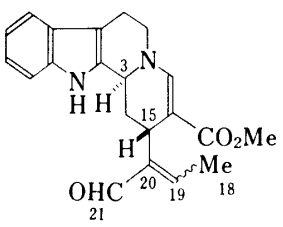
A Rubiaceous plant, *Uncaria rhynchophylla* Miq., is one of the original plants of the important Chinese crude drug, Gōu téng (鈎藤).[2] The constituents of the plant have been studied for a long time, but the studies were focused mostly on the tertiary indole alkaloids.[3] Since hot water decoctions of the crude drugs are usually used for therapeutic purposes in traditional Chinese medicine, a study of the water-soluble constituents of such plants seemed to us to be essential. The present paper deals with a study on the glycosides and other relatively polar constituents of *Uncaria rhynchophylla* Miq.

The leaves of the plant were extracted with hot methanol. The aqueous solution of the extract was washed with *n*-hexane and benzene successively and the water layer was shaken with *n*-butanol to give a fraction which consisted of glycosides and other constituents freed from the more water-soluble substances. The *n*-butanol fraction, after removal of the solvent, was dissolved in pH 8.9 borate buffer and extraction was done with ethyl acetate in the manner described by Brown.[4] Compound A (I) was isolated when the residue obtained by removal of the solvent from the ethyl acetate layer was treated with methanol. The mother liquor was fractionated by silica gel column chromatography and preparative thin layer chromatography (TLC) to give compounds B (II), C (III), and D (IV) together with several of the expected tertiary bases,[3] *i.e.* rhynchophylline (V), corynoxeine (VI) and isocorynoxeine (VII).

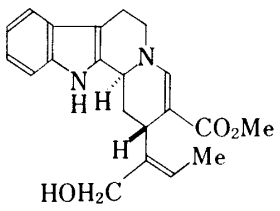
Compound A (I), mp 240—245°C, $C_{21}H_{22}N_2O_3$, was concluded to be vallesiachotamine on the basis of the characteristic ultraviolet absorption (UV) spectrum[5] and other spectral and chemical properties. In fact, the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectra of compound A and its $NaBH_4$ reduction product were superimposable on the authentic spectra of vallesiachotamine (I)[5] and dihydrovallesiachotamine (VIII), respectively.[5b] Although the ^{1}H-NMR spectrum of the mother liquor of recrystallization of compound A (I) revealed the presence of isovallesiachotamine (IX),[5c] pure (IX) could not be isolated.

Compound B (II), mp 208—212°C, was a glycoside with the molecular formula $C_{26}H_{30}N_2O_8$. Acetylation of II with acetic anhydride in pyridine gave a tetraacetate (X) which showed the molecular ion peak at *m/z* 666 in the mass spectrum (MS). The ^{1}H-NMR spectrum of the acetate (X) was identical with that of authentic vincoside lactam tetraacetate,[6] and therefore compound B (II) was concluded to be vincoside lactam.[6]

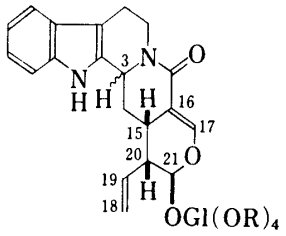
Compound C (III) was obtained as an amorphous powder and the spectral data of (III) and its acetate (XI) showed good coincidence with the data reported for strictosamide (III)[6] and its acetate (XI).[6] In particular, an abnormally highly shielded acetyl methyl signal at δ 1.21 in the ^{1}H-NMR spectrum of the acetate (XI) was quite characteristic of strictosamide tetraacetate (XI).[7] The ^{1}H-NMR spectrum of authentic XI was superimposable on that of compound C tetraacetate, and therefore compound C was concluded to be strictosamide (III).



I : $\Delta^{19,20}$: *E*
IX : $\Delta^{19,20}$: *Z*



VIII



II : 3β-H, R=H
III : 3α-H, R=H
X : 3β-H, R=Ac
XI : 3α-H, R=Ac

Chart 1

The name rhynchophine was given to a new compound, compound D (IV), which was obtained as an amorphous powder. The UV spectrum, showing absorption maxima at 225, 284, 291 and 328 nm, demonstrated the presence of indole ring, β-alkoxy acrylic amide and oxygenated cinnamic ester chromophores. The ^{1}H-NMR spectrum of the acetate (XII) showed four acetyl-methyl signals; one at δ 2.32 was assignable to a phenolic and three at δ 2.0 to alcoholic acetyl groups. Rhynchophine (IV) gave vincoside lactam (II)[6] and methyl ferulate (XIII) on treatment with sodium methoxide in methanol; thus IV was proved to be a ferulate

Table I. Carbon Shifts of Rhynchophine (IV) and Vincoside Lactam (II)[a]

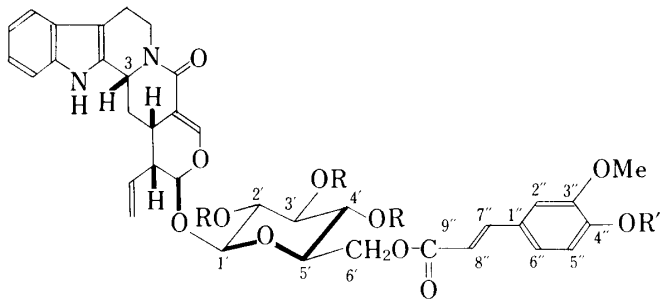
	II	IV[d]		II	IV[d]
C-2	134.6	134.7	C-22	163.3	163.2
C-3	53.3	53.4	C-1′	100.4	100.8
C-5	39.9	39.8	C-2′	74.9	74.8
C-6	21.6	21.6	C-3′	78.3[c]	78.1
C-7	108.5[b]	108.7	C-4′	71.3	71.2
C-8	127.6	127.6	C-5′	78.8[c]	75.8
C-9	118.5	118.6	C-6′	62.5	64.3
C-10	119.6	119.6	C-1″		126.4
C-11	121.9	121.9	C-2″		111.4
C-12	111.7	111.7	C-3″		150.4
C-13	137.7	137.7	C-4″		151.1
C-14	32.0	31.9	C-5″		116.8
C-15	26.8	26.9	C-6″		125.0
C-16	108.7[b]	108.7	C-7″		145.7
C-17	147.7	147.6	C-8″		115.0
C-18	119.6	119.6	C-9″		167.5
C-19	133.3	133.4	O-CH_3		55.9
C-20	43.7	43.8			
C-21	96.8	97.3			

a) δ-Values in ppm downfield from TMS measured in pyridine-d_5.
b) Assignments may be reversed.
c) Assignments may be reversed although those given here are preferred.
d) For the assignment of the carbons on the feruloyl moiety, see ref. 13).

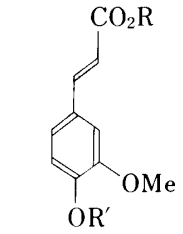
(3-methoxy 4-hydroxy cinnamate) of II. The site of the ester linkage was determined by means of ^{13}C-NMR.[8] Table I shows the ^{13}C-NMR data for rhynchophine (IV) and vincoside lactam (II). The assignments of the carbon signals of II were made on the basis of ^{13}C-assignments of vincoside lactam tetraacetate reported by Wenkert *et al.*[9]

Comparison of the chemical shifts of the glucose carbons of IV and II revealed that the ferulate group was located at $C_{(6')}$; the signal due to $C_{(6')}$ of IV appeared at δ 64.3, deshielded by 1.8 ppm as compared to the chemical shift of the corresponding carbon of II, while the signal due to $C_{(5')}$ of IV was observed at δ 75.8, shielded by 3.0 ppm as compared with that of the corresponding carbon of II.[8] These data indicated that IV was 6′-feruloyl vincoside lactam.

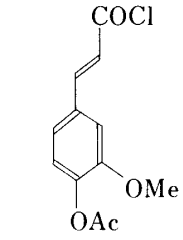
The partial synthesis of rhynchophine (IV) was then carried out. Vincoside lactam (II) was condensed with one molar equivalent of *O*-acetylferuloyl chloride (XV) in pyridine to give an amorphous powder (XVI). The ^{1}H-NMR signal at δ 4.51 (2H) was ascribable to the protons on $C_{(6')}$, which carries an acyloxyl group; this observation proved that the acylation took place selectively at the desired position. Removal of the phenolic acetyl group from the ferulate moiety was achieved by the use of sodium methoxide in methanol. The resulting compound was identical with the natural rhynchophine as evidenced by comparison of the ^{1}H-NMR and IR spectra and TLC behavior. In 1971, Brown isolated from *Adina rubescens* (Rubiaceae) an esterified glucoalkaloid, rubescine (XVII), which had a vincoside lactam structure possessing a caffeoyl residue at $C_{(3')}$ of the glucose moiety.[10]



IV : R=R′=H
XII : R=R′=Ac
XVI : R=H, R′=Ac



XIII : R=Me, R′=H
XIV : R=H, R′=Ac



XV

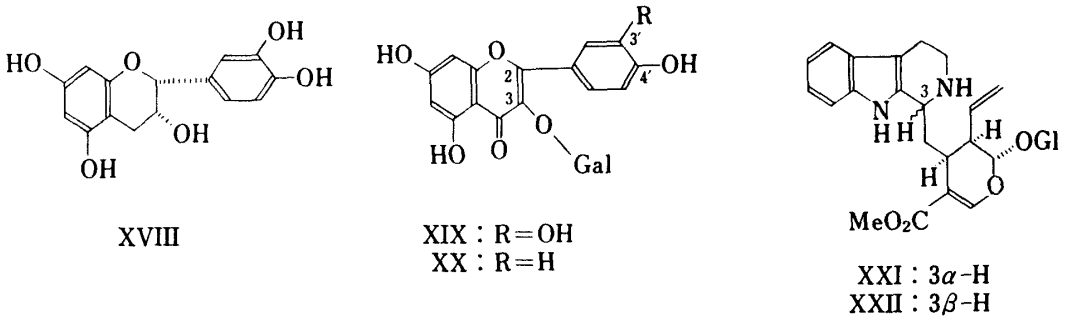
Chart 2

Three additional constituents were isolated when the butanol-soluble fraction of the plant extract, without treatment with borate buffer, was subjected to chromatographic separation.

Compound E (XVIII), mp 231—233°C, $C_{15}H_{14}O_6$, $[\alpha]_D = -58°$, was shown to be (−)-epicatechin by direct comparison with a commercial specimen.

Compound F (XIX), mp 232—235°C, $C_{21}H_{20}O_{12}$, gave quercetin and galactose on acid hydrolysis. The β-glycosidic linkage was indicated by the ^{1}H-NMR signal of $C_{(1')}$H at δ 5.95 which was observed as a doublet with a coupling constant of 9 Hz. These and other data suggested XIX to be hyperin (quercetin-3-*O*-β-D-galactoside).[11a] Comparison of the physical and spectral data including ^{13}C-NMR[11b] confirmed the identity of compound F as hyperin.

Compound G (XX), mp 231—232°C, $C_{21}H_{20}O_{11}$, was concluded to be kaempferol glycoside on the basis of UV and NMR evidence. Direct comparison with an authentic specimen proved XX to be trifolin.[12]



XVIII

XIX : R=OH
XX : R=H

XXI : 3α-H
XXII : 3β-H

Chart 3

It has been reported that vallesiachotamines (I, IX) are easily formed from a glucoalkaloid, strictosidine (XXI), even in the process of routine extraction.[7] Vincoside lactam (II) and strictosamide (III) are also known to be formed from vincoside (XXII) and strictosidine (XXI), respectively, under fairly mild conditions.[6,7] Therefore we cannot exclude the possibility that at least a part of these constituents can be secondarily formed during the extraction and separation processes. Attempts to isolate the possible genuine glucoalkaloids, (XXI) and (XXII), are now under way.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were obtained on a JEOL MH-100 (100 MHz) spectrometer with $CDCl_3$ as the solvent unless otherwise specified. The chemical shifts are presented in δ (ppm) from the internal standard (TMS). ^{13}C-NMR spectra were run on a JEOL PFT-100 spectrometer operating at 25.15 MHz in pyridine-d_5 and the chemical shifts are presented in δ (ppm) from the internal standard (TMS). Mass spectra were recorded on a Hitachi RMU-60 or RMU-7M spectrometer. UV spectra were obtained on a Hitachi ESP-3T spectrometer using ethanol as the solvent. The analytical TLC work was done on pre-coated plates, Silica Gel 60 F_{254}, Merck. Silica Gel 60 (Merck), 70—230 mesh and 230—400 mesh, was used for column chromatography.

Extraction and Separation of the Constituents of *Uncaria rhynchophylla* Miq.——The fresh leaves of *Uncaria rhynchophylla* Miq. (2.35 kg) collected at Owase, Mie Prefecture, in September 1980, were extracted with MeOH to give a residue (494 g). Water was added to the extract and the precipitate was removed by centrifugation. The supernatant (2 l) was washed with *n*-hexane, and then with benzene. The water layer was extracted with *n*-BuOH, and the extract was concentrated to leave residue (60 g), which was dissolved in borate buffer of pH 8.9. Repeated extraction of this solution with hot AcOEt and concentration of the extracts afforded 16.4 g of a residue.

The above residue was treated with MeOH and compound A (I) (466 mg) was obtained. The following spectral and chemical evidence proved it to be vallesiachotamine (I). The ^{1}H-NMR spectra of compound A (I) and its $NaBH_4$ reduction product (VIII) were superimposable on those of vallesiachotamine and dihydrovallesiachotamine (copies of the latter spectra were kindly provided by Dr. Smith, Manchester University).

The mother liquor of the crystals was subjected to silica gel column chromatography. Elution with $CHCl_3$–MeOH (9: 1) gave a mixture of vallesiachotamine (I) and isovallesiachotamine (IX) as a heavy syrup, and the ^{1}H-NMR spectrum revealed the product ratio to be approximately 3: 4. The next fraction eluted with the same solvent mixture was subjected to flash column chromatography on silica gel. Elution with $CHCl_3$–AcOEt (7: 3) gave rhychophylline (V) (46 mg), corynoxeine (VI) (151 mg) and isocorynoxeine (VII) (235 mg). Isocorynoxeine (VII) was derivatized to the perchlorate, mp 172—185°C, which was proved to be identical with an authentic specimen. Corynoxeine (VI) and rhynchophylline (V) were also identical with authentic specimens.

Compounds B to D were successively eluted from the SiO_2 column with the solvent system of $CHCl_3$–MeOH (8: 2). Each of the components was purified by further chromatography over SiO_2 or by flash column chromatography over SiO_2 using $CHCl_3$–MeOH (85: 15) as the eluent.

Compound A (Vallesiachotamine) (I)——mp 240—245°C (from benzene); *Anal.* Calcd for $C_{21}H_{22}N_2O_3$: C, 72.00; H, 6.29; N, 8.00. Found: C, 71.83; H, 6.36; N, 7.88. MS *m/z*: 350 (M^+, 72%) and 279 (base peak). UV λ_{max}^{MeOH} nm (log ε): 223 (4.69), 286 (4.51), and 291 (4.54). $[\alpha]_D^{20}$ +180° (c=1.0, $CHCl_3$). ^{1}H-NMR $\delta_{DMSO\text{-}d_6}$: 1.99 (3H, d, J=7 Hz, $C_{(18)}H_3$), 3.52 (3H, s, CO_2Me), 4.35 (1H, br d, J=9 Hz, $C_{(3)}H$), 6.70 (1H, q, J=7 Hz, $C_{(19)}H$), 7.65 (1H, s, $C_{(17)}H$) and 9.32 (1H, s, $C_{(21)}H$). IR ν_{max}^{KBr} cm^{-1}: 3225 (NH); 1680, 1660 (conj. C=O); 1640, 1620 (conj. C=C).

Compound B (Vincoside Lactam) (II)——mp 208—212°C (from MeOH–H_2O) (890 mg). *Anal.* Calcd for $C_{26}H_{30}N_2O_8 \cdot 2.5H_2O$: C, 57.45; H, 6.49; N, 5.15. Found: C, 57.30; H, 6.26; N, 5.04. $[\alpha]_D^{29}$ −90° (c=0.33, MeOH). UV λ_{max} nm (log ε): 227 (4.60), 274 (4.05), 282 (3.99) and 290 (3.87). IR ν_{max}^{KBr} cm^{-1}: 3600—3000 (br, OH), 1660 (lactam C=O), and 1580 (conj. C=C). CD $\lambda_{max.\ min}$ nm ($\Delta\varepsilon$): 216 (+14.2), 234 (−14.2) and 268 (−5.9).

Compound B Tetraacetate (X): Amorphous powder. MS m/z: 666 (M^+, 100%). ^{1}H-NMR δ: 1.46 (1H, m, $C_{(14\alpha)}H$), 1.98, 1.99, 2.01 and 2.08 (each 3H, s, OAc×4); 2.12 (1H, m, $C_{(14\beta)}H$), 2.5—3.1 (5H, m, $C_{(5\beta)}H$, $C_{(6)}H$, $C_{(15)}H$ and $C_{(20)}H$); 3.76 (1H, m, $C_{(5')}H$); 4.12 and 4.32 (2H, m, $C_{(6')}H_2$); 4.6—5.6 (10H, m, $C_{(3)}H$, $C_{(5\alpha)}H$, $C_{(18)}H$, $C_{(19)}H$, $C_{(21)}H$, $C_{(1')}H$, $C_{(2')}H$, $C_{(3')}H$, and $C_{(4')}H$); 7.0—7.6 (5H, m, arom. H×4 and $C_{(17)}H$); 8.18 (1H, s, NH). The ^{1}H-NMR spectrum of compound B tetraacetate (X) was superimposable on that of vincoside lactam tetraacetate.

Compound C (Strictosamide) (III)——Amorphous powder (589 mg). $[\alpha]_D^{26}$ −47° (c=0.6, MeOH). UV λ_{max} nm (log ε): 225 (4.39), 285 (3.82) and 292 (3.75). IR ν_{max}^{KBr} cm^{-1}: 3650—3000 (OH, NH); 1650 (lactam C=O); 1580 (conj. C=C). CD $\lambda_{max.\ min}$ nm ($\Delta\varepsilon$): 270 (+4.02).

Compound C Tetraacetate (XI): Amorphous powder. MS m/z: 666 (M^+, 100%). $[\alpha]_D^{28}$ −50° (c=0.4, $CHCl_3$). ^{1}H-NMR δ: 1.21, 1.86, 1.96 and 2.04 (each 3H, s, OAc×4); 2.14 (2H, m, $C_{(14)}H_2$); 2.4—3.2 (4H, m, $C_{(6)}H_2$, $C_{(15)}H$ and $C_{(20)}H$); 3.65 (1H, m, $C_{(5')}H$); 4.16 (2H, m, $C_{(6')}H$); 4.6—5.6 (11H, m, $C_{(4')}H$, $C_{(21)}H$, $C_{(2')}H$, $C_{(3')}H$, $C_{(3)}H$, $C_{(5)}H$, $C_{(1')}H$, $C_{(18)}H$ and $C_{(19)}H$); 7.0—7.6 (5H, m, arom. H×4 and $C_{(17)}H$) and 8.06 (1H, s, NH). The ^{1}H-NMR spectrum of compound C tetraacetate (XI) was identical with that of strictosamide tetraacetate.

Compound D (Rhynchophine) (IV)——Amorphous powder (30 mg). $[\alpha]_D^{27}$ −45° (c=0.7, MeOH). UV λ_{max} nm (log ε): 225 (4.62), 284 (4.17), 291 (4.18) and 328 (4.18). IR ν_{max}^{KBr} cm^{-1}: 3700—3000 (br, OH, NH); 1700 (ester C=O); 1650 (amide C=O). CD $\lambda_{max.\ min}$ nm ($\Delta\varepsilon$): 232 (−6.8) and 268 (−2.9). ^{1}H-NMR δ_{CD_3OD}: 7.64 (1H, s, J=15 Hz) and 6.36 (1H, d, J=15 Hz) (AB-type, olefinic protons on feruloyl moiety); 3.85 (3H, s, arom.-OMe).

Compound D Tetraacetate (XII): Acetylation of compound D (rhynchophine) (IV) (20 mg) with acetic anhydride in pyridine gave the acetate (XII) (5 mg), after purification of the reaction product by preparative TLC. Amorphous powder. $[\alpha]_D^{28}$ −30° (c=0.4, $CHCl_3$). UV λ_{max} nm (log ε): 226 (4.48), 283 (4.27), 290 (4.25) and 312 (4.01). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (br, acetyl and feruloyl C=O); 1665 (amide C=O); 1600 (conj. C=C). CD $\lambda_{max.\ min}$ nm ($\Delta\varepsilon$): 233 (−11.4) and 268 (−3.65). ^{1}H-NMR δ: 2.00 (9H, s, OAc×3); 2.32 (3H, s arom.-OAc); 3.88 (3H, s, arom.-OMe); 4.36 (2H, m, $C_{(6')}H_2$); 6.38 (1H, d, J=15 Hz) and 7.66 (1H, d, J=15 Hz) (AB type, olefinic protons of feruloyl group); 8.02 (1H, br s, NH).

Methanolysis of Compound D (Rhynchophine) (IV)——Compound D (rhynchophine) (IV) (49 mg) was dissolved in absolute MeOH (3 ml) and 1 ml of 0.08 N NaOMe in MeOH was added. To complete the reaction, 0.4 ml of the above NaOMe solution was added. Dilution of the reaction mixture with MeOH followed by treatment with ion exchange resin (Amberlite IR-120B) gave a crude reaction product, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$ afforded methyl ferulate (XIII) (4 mg) which was shown to be identical with an authentic synthetic sample by comparison of the MS, ^{1}H-NMR, UV and IR spectra. Elution with $CHCl_3$–MeOH (95: 5) yielded vincoside lactam (II) (3 mg) as needles; this product was identical with the natural product on the basis of mixed mp determication and comparison of the IR spectra.

Synthesis of Compound D (Rhynchophine) (IV)——*O*-Acetyl ferulic acid (XIV) (100 mg) was chlorinated by the use of $SOCl_2$ (0.4 ml) under reflux. The resulting acid chloride was dissolved in THF (5 ml) and the solution (2 ml) was added to a pyridine (10 ml) solution of vincoside lactam (II) (100 mg) at −10°C. The solution was stirred at room temperature overnight. Removal of the solvent afforded a crude residue, which was diluted with water. The aqueous solution was extracted with AcOEt. Removal of the solvent gave a residue which was subjected to preparative TLC to give 6′-(*O*-acetylferuloyl)-vincoside lactam (XVI) as an amorphous powder (45 mg). ^{1}H-NMR δ: 2.23 (3H, s, OAc); 3.76 (3H, s, OMe); 6.48 (1H, d, J=15 Hz) and 7.62 (1H, d, J=15 Hz) (AB type, olefinic protons on feruloyl group); 4.51 (2H, m, $C_{(6')}H_2$).

A solution of XVI (34 mg) in MeOH (5 ml) was treated with 0.1 N NaOMe (0.1 ml), and the reaction mixture was stirred at room temperature for 16 h. After dilution of the solution with MeOH, de-salting was done with Amberlite IR 120B. The resulting product was purified by preparative TLC to give 6′-feruloyl vincoside lactam (IV) which was proved to be identical with compound D (rhynchophine) by comparison of the TLC behavior and ^{1}H-NMR spectra. Amorphous powder. MS m/z: 674 (M^+, 17%) and 177 (base peak). *Anal.* Calcd for $C_{36}H_{38}N_2O_{11} \cdot 1.5H_2O$: C, 61.62; H, 5.89; N, 3.99. Found: C, 61.74; H, 5.73; N, 3.97.

Isolation of Phenolic Constituents of *Uncaria rhynchophylla* Miq.——Phenolic components wereisolated from the above *n*-BuOH fraction of the crude extract when the crude material was subjected to SiO_2 column chromatography without borate buffer treatment. From 20 g of the *n*-BuOH fraction, 252 mg of compound E, 711 mg of compound F, and 313 mg of compound G were obtained.

Compound E ((−)-Epicathechin) (XVIII)——mp 231—233°C (dec.). $[\alpha]_D^{23}$ −58° (c=1.0, Me_2CO–H_2O 1: 1). *Anal.* Calcd for $C_{15}H_{14}O_6 \cdot 1/2H_2O$: C, 60.19; H, 5.05. Found: C, 60.39; H, 4.86. Direct comparison showed that this compound was (−)-epicatechin.

Compound F (Hyperin) (XIX)——mp 232—235°C. Yellow crystals from MeOH–H_2O. $[\alpha]_D^{21}$ −82° (c=

1.0, pyridine). UV λ_{max} nm (log ε): 205 (4.62), 258 (4.35) and 365 (4.27). IR ν_{max}^{KBr} cm^{-1}: 3470, 3280 and 1660. *Anal.* Calcd for $C_{21}H_{20}O_{12}\cdot 2H_2O$: C, 52.07; H, 4.99. Found: C, 52.16; H, 4.55. These and other spectral and physical data, together with a comparison of the ^{13}C-NMR data with those given in the literature,[11b] proved that compound F was hyperin.

Compound G (Trifolin) (XX)——mp 231—232°C (dec.) (yellow crystals from MeOH–H_2O). $[\alpha]_D^{18}$ −77° (c=0.3, pyridine). UV λ_{max} nm (log ε): 208 (4.53), 267 (4.34), 300 (sh) (4.07) and 353 (4.28). IR ν_{max}^{KBr} cm^{-1}: 1660. ^{1}H-NMR δ: 6.08 (1H, d, J=9 Hz, $C_{(1'')}$H), 6.64 (2H, s, $C_{(6)}$H and $C_{(8)}$H), 7.20 (2H, d, J=9 Hz, $C_{(3')}$H and $C_{(5')}$H) and 8.42 (2H, d, J=9 Hz, $C_{(2')}$H and $C_{(6')}$H). Direct comparison (mixed fusion and comparison of the IR spectra) showed that compound G was trifolin.

Acknowledgement We are grateful to Dr. R.T. Brown, Manchester University, England, for the kind gift of ^{1}H-NMR and IR spectra of vincoside lactam tetraacetate and strictosamide tetraacetate, and for other valuable information. We also thank Dr. G.N. Smith, Manchester University, England, for providing the ^{1}H-NMR spectra of vallesiachotamine, isovallesiachotamine and the corresponding dihydro derivatives. An authentic sample of trifolin was given by Dr. S. Mihashi, Tokyo College of Pharmacy, to whom our thanks are due. We also thank Mr. M. Kawaguchi for his assistance in collecting the plant material at Owase, Mie Prefecture.

References and Notes

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