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Aporphine and Tetrahydrobenzylisoquinoline Alkaloids from the Seeds of *Zizyphus vulgaris* var. *spinosus*

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Abstract□From the seeds of *Zizyphus vulgaris* var. *spinosus*, aporphine alkaloids: nuciferine, N-methylasimilobine, nornuciferine, norisocorydine, caaverine and tetrahydrobenzylisoquinoline alkaloid: (+)-coclaurine were isolated and identified. Zyzyphusine, a new quaternary aporphinium alkaloid from butanol soluble fraction was isolated and characterized by spectral data.

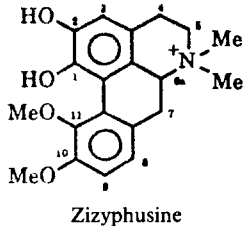
Keywords□*Zizyphus vulgaris* var. *spinosus*. Rhamnaceae, sedative activity, aporphinoid, tetrahydrobenzylisoquinoline, nuciferine, N-methylasimilobine, nornuciferine, norisocorydine, caaverine, coclaurine, zizyphusine.

It has been reported[1] that alkaloids are the sedative principles of the seeds of *Zizyphus vulgaris* Lamark var. *spinosus* Bunge which have been used as the most important hypnotic agent in Chinese medicine. Eight cyclic peptide alkaloids have been isolated as a series of sedative principles.[2] This paper is to describe the details of characterization of aporphinoids as the other series of sedative ingredients, together with tetrahydrobenzylisoquinoline alkaloid and one new quaternary ammonium type alkaloid, zizyphusine from the butanol soluble fraction.

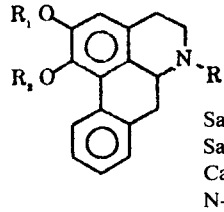
A new alkaloid tentatively named as zizyphusine, mp 214-216 °C, *m/z* 425 [M^+] was isolated from the butanol soluble, so called, saponin fraction by silicagel column chromatography using ammonia containing eluents or it could also be obtained as a single component from the water layer when the butanol fraction was acetylated then partitioned between chloroform and water.

It gave a yellow-red color with Dragendorff's reagent, red-violet with Pauly's reagent and deep red color with $FeCl_3$. It is highly soluble in water and even its acetate is water soluble and would not move into organic solvents except *n*-butanol at any pH.

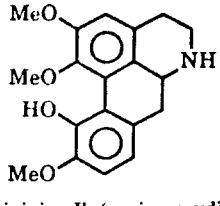
When exposed to air or light, it easily turns brown. The nature of the N is quaternary[3] because the compound (i) gives a positive response with citric acid and Ac_2O, (ii) did not form methiodide on treatment with MeI and (iii) showed ^1H NMR



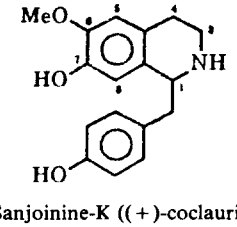
Zizyphusine



Sanjoinine-E(nuciferine): $R = CH_3$, $R_1 = R_2 = CH_3$
Sanjoinine-Ia(nornuciferine): $R = H$, $R_1 = R_2 = CH_3$
Caaverine: $R = H$, $R_1 = CH_3$, $R_2 = H$
N-Methylasimilobine: $R = CH_3$, $R_1 = H$, $R_2 = CH_3$



Sanjoinine-Ib (norisocorydine)



Sanjoinine-K ((+)-coclaurine)

signals at δ 2.8 and 3.3 ppm corresponding to each three protons characteristics of N,N-dimethyl groups. Its UV spectra showed λ_{max} at 227, 227.5, 320 nm which suggested a 1,2,10,11-tetrasubstituted aporphine skeleton.[4] The ^{1}H NMR spectrum of zizyphusine exhibited signals at δ 3.68 (6H, s, 2xOMe), 6.49 (s, 1H, C3-H), 6.36 (1H, d, J = 7.8 Hz, C9-H), 6.58 (1H, d, J = 7.8 Hz, C8-H). Other aliphatic protons appeared in the region between δ 3.2 and 2.6.

The presence of two phenolic OH groups in zizyphusine was confirmed by the formation of two O-acetate (δ 2.14, 2.17, each 3H, s) from zizyphusine by treatment with Ac_2O-pyridine at room temperature. The ^{1}H NMR of acetate showed that the C-3 proton had shifted downfield (δ 6.49→δ 7.07), which suggested the position of one OH group was at the C-2 position. The AB double doublets of C-8 and C-9 protons suggested the position of one OMe at C-11[5]

Strong chelating characteristic of zizyphusine with $FeCl_3$ (deep red color) suggested a catechol system of two phenolic OH groups. Consequently the position of the other OH group at the C-1 position and one OMe group at C-10 position were established. The structure of zizyphine was proposed as 1,2-dihydroxy-10,11-dimethoxy-N-methyl aporphinium. ^{13}C NMR spectrum of zizyphusine acetate (DMSO-d_6) as assigned by referring the data[6] of related compounds and by attached proton test (Fig. 1).

Sanjoinine-E, mp 166°C, [M$^+$] m/z 295 ($C_{19}H_{21}NO_2$) gave a positive Dragendorff's test (redish brown), and showed mass fragmentation of a typical aporphine alkaloid pattern.[7] The ^{1}H NMR exhibited the presence of two methoxyl, an N-me-

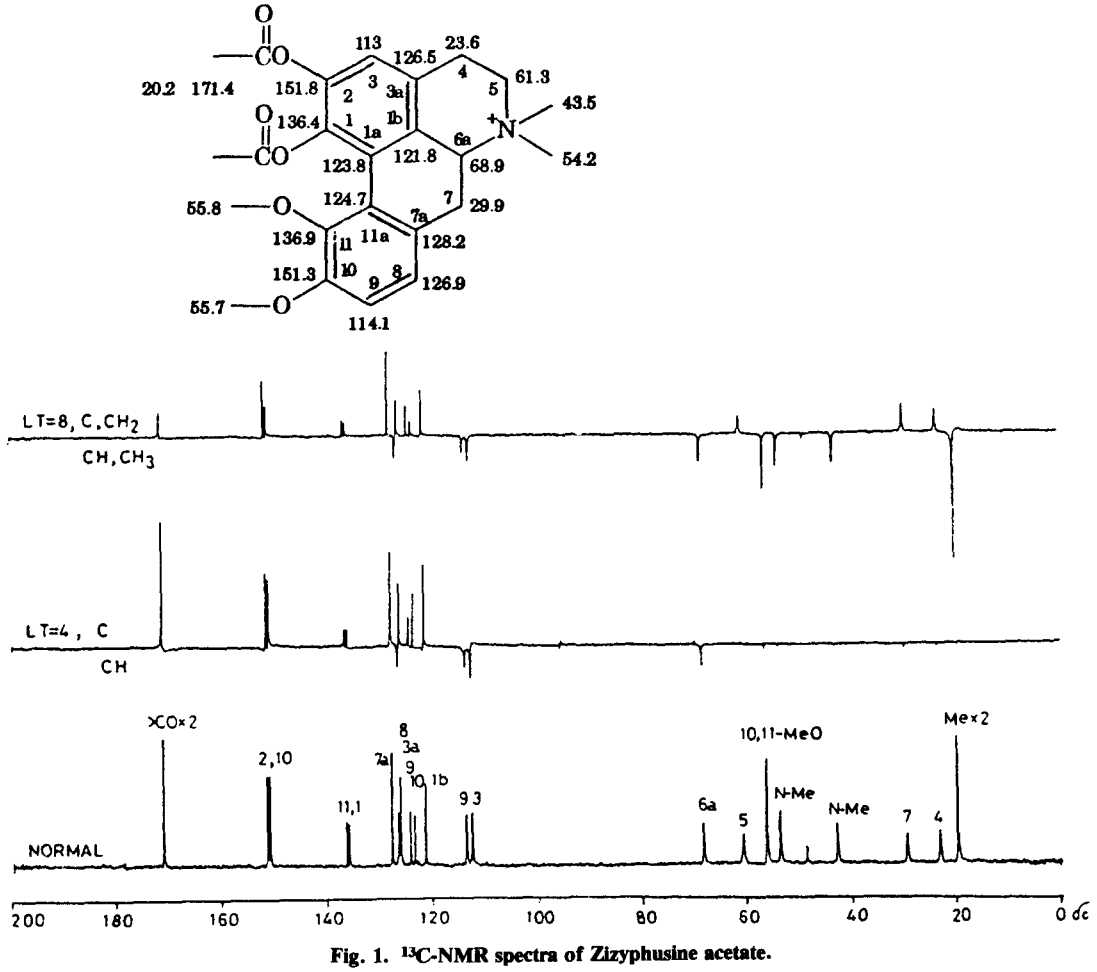


Fig. 1. ^{13}C-NMR spectra of Zizyphusine acetate.

thyl, seven aliphatic protons (δ 3.2-2.82) and five aromatic protons. Aromatic protons: one singlet at δ 6.63 (1H), a multiplet at δ 8.35 (1H) and a multiplet at δ 7.36-7.26 (3H) were respectively as C3-H, C11-H, and C8-H, C9-H, C10-H of aporphine skeleton.[8] From these facts sanjoinine-E was identified as nuciferine isolated previously from other plants.[9,10]

The compound identifiable as N-methylasimilobine was isolated as minor component. It showed a positive Dragendorff's test(yellowish brown) and a red color with Pauly's reagent. Pauly positive reaction suggested the presence of phenolic hydroxyl group whose *ortho* or *para*-position is unsubstituted. Its ^{1}H NMR spectra showed one N-methyl at δ 2.53 and one methoxyl at δ 3.56 of high field shift due to its position C-1[8]. One singlet at δ 6.68 (1H, C3-H), one multiplet at δ 8.26 (1H, C11-H) and one multiplet at δ 7.31-7.20 (3H, C8, C9, C10-11) with aliphatic protons at δ 3.45-2.60 (7H) were characteristic of aporphine alkaloid with no substituents in ring D. These facts including mass spectrum were identical with those of N-methylasimilobine from *Colubrina faralaotra*.[11]

Sanjoinine-Ia, mp 155-157 °C, showed a [M$^+$] at *m/z* 281. Its ^{1}H NMR spectra of one proton multiplet at 8.37, three protons multiplet at δ 7.37-7.23, one proton singlet at δ 6.55 and aliphatic protons at δ 3.09-2.72 (7H) were characteristic of aporphine alkaloid with no substituents in ring D. These data with mass fragmentations were identical with those of nornuciferine.[12] Its acetate prepared with acetic anhydride and pyridine showed IR absorption at 1630 cm^{-1} indicating N-acetate (δ 2.19, s, 1H). Its ^{1}H NMR spectrum and mass spectrum were identical with N-acetyl nornuciferine isolated from natural sources.[13,14] Consequently sanjoinine-Ia was identified as nornuciferine.

Sanjoinine-Ib, mp 184 °C, gave a positive Dragendorff's test(yellowish brown) and Pauly's test. The UV spectrum λ_{max} 224, 268, 309 nm suggested a 1,2,10,11-tetrasubstituted aporphine skeleton.[4] Its ^{1}H NMR spectrum showed three methoxyl at δ 3.73 (3H, s) and 3.91 (6H, s), one aromatic at δ 6.73 (1H, s, CH-3) and two aromatic protons as a singlet at δ 6.85 which were separated into AB quartet at δ 6.72 (C8-H) and 6.92 (C9-H) with J = 8.2 Hz when the compound was acetylated. This fact showed a good agreement to the previously established fact that the C8-H and C9-H protons showed a singlet in case of free hydroxyl at C11 position, while they split into AB quartet in case of C11-OCH_3. The mass spectrum showed a typical fragmentation of noraporphine and was identical with norisocorydine.[15] Its acetate prepared by acetic anhydride and pyridine showed one N-acetyl (δ 2.16, IR λ_{max} 1630 cm^{-1}) and one O-acetyl (δ 2.25, IR V_{max} 1740 cm^{-1}). The mass spectrum followed a typical fragmentation of N-acetylaporphine. So sanjoinine-Ib was identified as norisocorydine.

The alkaloid identified as caaverine, mp 204 °C, showed a typical ^{1}H NMR of aporphinoid. Its acetate showed one N-acetyl (δ 2.19, 3H, s), one O-acetyl (δ 2.30, 3H, s) and one singlet at δ 6.86 (1H, s) attributable to C3-H which did not shift much ($\Delta\delta$ 0.07) after acetylation. This was suggestive that the position of the hydroxyl group at the C-1 position. Mp and optical rotation of this compound (mp 204 °C, $[\alpha]_D$-80 °) were almost same with those of caaverine (mp 208 °C, $[\alpha]_D$-89 °)[16] rather than those of asimilobine (mp 177-179 °C, $[\alpha]_D$ 203 °).[17]

Sanjoinine-K, mp 159-161 °C gave a positive reaction with Dragendorff's reagent and Pauly's reagent. The ^{1}H NMR spectrum showed three D_2O exchangable protons at δ 9.41 and 8.90, one methoxyl at δ 3.74, singlets at δ 6.55 (1H) and 6.73 (1H), AB double doublets at δ 6.74 and 7.13, triplet at δ 4.47 (1H) and aliphatic protons at δ 3.3-2.8 (6H). This suggested that sanjoinine-K was tetrahydrobenzylisoquinoline alkaloid.[18] The position of one methoxyl group at C-7 was ruled out by its low chemical shift (δ 3.74) while C7-OCH_3 would be expected at δ 3.55-3.51 due to diamagnetic ring current of benzyl benzene ring. The negative reaction with $FeCl_3$ indicated two phenolic hydroxyls were not in a catechol type. This was further supported by a typical mass fragmentation of tetrahydrobenzylisoquinoline.[7] Sanjoinine-K was identified as (+)-coclaurine because of $[\alpha]_D$ + 35 °.

EXPERIMENTAL METHODS

Melting points were recorded on a Mitamura Riken Heat Block Model-MRK and are uncorrected. Optical rotations were measured on a Rudolph Autopol^R III automatic polarimeter. UV and IR spectra were recorded on a Gilford System 2600 UV-VIS spectrophotometer and a Perkin-Elmer 281 B spectrophotometer, respectively. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Model FT 80A NMR spectrometer (80 MHz, 20 MHz) with TMS at internal standard. Mass spectra were taken on a Hewlett Packard Model HP 5985 B GC/MS system. (70 eV, 30 eV).

Extraction and Isolation of Alkaloids

Crushed seeds of *Zizyphus vulgaris* var. *spinosus* (30 kg × 2, purchased on a Market) were extracted with boiling hexane (90*l* × 2) and MeOH (90*l* × 2) successively. MeOH extract (4.8 kg) was suspended in water (10*l*) and extracted with Et_2O (15*l* × 4) and *n*-BuOH (15*l* × 3) successively. With hexane extract (17 kg) and Et_2O extract, a crude alkaloid fraction was prepared by a usual method. Namely extraction with 5% HCl and basification with NH_4OH (pH 10) and then $CHCl_3$ extraction yielded alkaloid fraction (5.3g, 20.1g from hexane Ex. and Et_2O Ex. respectively).

Isolation of Zizyphusine

Method A. BuOH Ex. (42g) was chromatographed over silicagel with $CHCl_3$-MeOH-H_2O (15:10:2.5) and Dragendorff's reagent positive fractions were collected. This fraction was re-charged over silicagel column, eluted with $CHCl_3$-MeOH-c-NH_4OH(6:3:1) and single spot fractions positive with UV, $FeCl_3$, Dragendorff's reagent and devoid of ninhydrin positive impurity yielded zizyphusine (320 mg, 6.2×10^{-3}% yield). mp 214-216 °C. $[\alpha]_D^{22}$ + 317°(c = 0.72, H_2O), UV λ_{max}nm (log ε): 227 (4.52), 277.5 (3.83), 320 (3.82). ^{1}H NMR (DMSO-d_6, δ ppm): 2.85 (3H, s, N-CH_3), 3.28 (3H, s, N-CH_3), 3.68 (6H, s, C10, C11-OCH_3 × 2), 5.0 (2H, br. s, OH × 2), 6.49 (1H, s, C3-H), 6.36 (1H, d, J = 7.8 Hz, C9-H), 6.58 (1H, d, J = 7.8 Hz, C8-H).

Method B. BuOH Ex. (48g) was acetylated with Ac_2O (200 m*l*) and pyridine (200 m*l*) at RT overnight. The residue obtained after evaporation of reagents was partitioned between $CHCl_3$ and water. Evaporation of water furnished 2.8g residue which was purified by silicagel column chromatography ($CHCl_3$-MeOH-H_2O, 3:1:0.1) to give zizyphusine acetate (780 mg, 9×10^{-3}%) in a single state. mp 184-186 °C. ^{1}H NMR (DMSO-d_6, δ ppm): 2.14 (3H, s, O-$COCH_3$), 2.17 (3H, s, O-$COCH_3$), 2.93 (3H, s, N-CH_3), 3.46 (3H, s, N-CH_3), 3.78 (3H, s, C11-OCH_3), 3.82 (3H, s, C10-OCH_3), 7.13 (1H, s, C3-H), 7.17 (1H, d, J = 7.8 Hz, C9-H), 7.35 (1H, d, J = 7.8 Hz, C8-H). ^{13}C NMR (DMSO-d_6, δ ppm): see Fig. 1. MS *m/z* (Rel. Int. %): 425 (M^+-CH_3COO, 7), 411 (16.4), 396 (4.2), 380 (1), 368 (1.3), 354 (3.9), 352 (7.5), 326 (1.6), 338 (0.5), 324 (0.5), 312 (2.1), 310 (3.1), 296 (2.9), 295 (1.3), 294 (0.5), 283 (3.6), 282 (2.1), 58 (100).

Alkaloid fraction (20g) of hexane and Et_2O Ex. was chromatographed over silicagel (4 × 32 cm) and successively eluted with $CHCl_3$-MeOH (70:1) 0.8*l*, [fr. 1, 5.1g], (50:1) 0.8*l* [fr. 2, 1.29g], (30:1) 0.8*l* [fr. 3, 1.75g], (10:1) 1.5*l* [fr. 4, 1.11g], (5:1) 0.8*l* [fr. 5, 5.12g] and (2:1) 1*l* [fr. 6, 1.67g].

Isolation of sanjoinine-E (nuciferine)

Fr. 2 (1.29g) and fr. 3 (1.75g) were chromatographed over silicagel with cyclohexane-EtOAc-MeOH (35:15:4) to give fr. 2, 3-1 (170 mg), fr. 2, 3-2 (980 mg), fr. 2, 3-3 (640 mg) and fr. 2, 3-4 (830 mg). Fr. 2, 3-3 (640 mg) was purified by preparative TLC on silicagel (cyclohexane-EtOAc-MeOH 35:15:4, Rf. 0.22) to give nuciferine as plates (60 mg, 2.7×10^{-5}% yield). mp 166 °C, $[\alpha]_D^{26}$-146.2° (c = 0.29, MeOH). ^{1}H NMR ($CDCl_3$, δ ppm): 2.58 (3H, s, N-CH_3), 3.20-2.28 (6H, m, C4, C5, C7-CH_2 × 3), 3.65 (3H, s, C1-OCH_3), 7.36-7.26 (3H, m, C8, C9, C10-H × 3), 8.35 (1H, m, C11-H). MS *m/z* (Rel. Int. %): 295 (M^+, 48.5), 294 (M^+-1, 91), 280 (M^+-15, 100), 264 (M^+-31, 81.4), 252 (M^+-43, 47.5), 237 (47.1), 221 (81.6), 178 (35.8), 165 (72.9).

Isolation of N-methylasimilobine

Fr. 4 (1.11g) was chromatographed over silicagel with cyclohexane-EtOAc-MeOH (30:15:4) to give Dragendorff's reagent and Pauly's reagent positive fraction (300 mg), which was subjected to preparative TLC (silicagel, $CHCl_3$-MeOH 30:1, developed twice) to yield N-methylasimilobine (Rf. 0.38, 3 mg, 5×10^{-6}% yield). mp 193-195 °C, $[\alpha]_D^{26}$-204°(c = 0.15, MeOH). ^{1}H NMR ($CDCl_3$, δ ppm): 2.53 (3H, s, N-CH_3), 3.45-2.60 (6H, m, C4, C5, C7-CH_2 × 3), 3.56 (3H, s, C1-OCH_3), 6.68 (1H, s, C3-H), 7.31-7.20 (3H, m, C8, C9, C10-H × 3), 8.26 (1H, m, C11-H). MS *m/z* (Rel. Int. %): 281 (M^+, 13), 280 (M^+-1, 13.8), 266 (M^+-15, 15.7), 250 (M^+-31, 19.5), 238 (M^+-43, 11.6), 237 (1.6), 222 (1.5), 206 (2.7).

Isolation of sanjoinine-Ia (nornuciferine) and sanjoinine-Ib (norisocorydine)

Fr. 5 (5.12g) was treated with 5% HCl and Et_2O. The acidic layer was alkalified with 5% NaOH (pH 12) and extracted with Et_2O to give nonphenolic alkaloid fraction (670 mg). The pH of water layer was adjusted to pH 9 with 10% HCl and $CHCl_3$ extraction gave phenolic alkaloid fraction (660 mg).

Nonphenolic alkaloid fraction (670 mg) was purified by silicagel flash column chromatography with $CHCl_3$-MeOH (20:1) to give sanjoinine-Ia (Rf. 0.25, 75 mg, 1.2×10^{-4}% yield). mp 155-157 °C, $[\alpha]_D^{26}$-140° (c = 0.15, EtOH), ^{1}H NMR ($CDCl_3$, δ ppm): 3.09-2.72 (6H, m, C4, C5, C7-CH_2 × 3), 3.68 (3H, s, C1-OCH_3), 3.89 (3H, s, C2-OCH_3), 6.65 (1H, s, C3-H), 7.37-7.23 (3H, m, C8, C9, C10-

H × 3), 8.37 (1H, m, C11-H). MS *m/z* (Rel. Int. %): 281 (M^+, 47.8), 280 (M^+-1, 80.6), 266 (M^+-15, 28.5), 252 (M^+-29, 7.5), 250 (M^+-31, 32.3), 237 (14.5), 221 (21.5), 178 (17.2), 165 (43.5).

Acetylation of sanjoinine-Ia (nornuciferine)

Sanjoinine-Ia (20 mg) was acetylated with Ac_2O and pyridine at RT for 20 hr. Reagents were removed by N_2 purgeing and yielded needles (18 mg) from $CHCl_3$. mp 205 °C, IR λ_{max} cm^{-1} (KBr): 1630 (N-$COCH_3$). ^1H NMR ($CDCl_3$, δ ppm): 2.19 (3H, s, N-$COCH_3$), 3.40-2.57 (6H, m, C4, C5, C7-CH_2× 3), 3.67 (3H, s, C1-OCH_3), 3.89 (3H, s, C2-OCH_3), 4.98 (1H, br, C6a-H), 6.68 (1H, s, C3-H), 7.66-7.01 (3H, m, C8, C9, C10-H × 3), 8.43 (1H, m, C11-H). MS *m/z* (Rel. Int. %): 323 (M^+, 5.3), 2.64 (M^+-59, 20.2), 252 (M^+-71, 25.3), 251 (M^+-72, 100), 2.37 (12.3), 221 (5.7).

Phenolic alkaloid fraction (660 mg) was purified by silicagel flash column chromatography and preparative TLC ($CHCl_3$-MeOH 20:1) to give Dragendorff's reagent and Pauly's reagent positive pure compound, sanjoinine-Ib (52 mg, 8.7×10^{-5}% yield). mp 184 °C, UV λ_{max} nm (log ϵ): 224 (4.77), 268 (4.12), 3.09 (3.76). ^1H NMR ($CDCl_3$, δ ppm): 3.34-2.83 (6H, C4, C5, C7-CH_2 × 3), 3.73 (3H, s, C1-OCH_3), 3.91 (6H, s, C2, C10-OCH_3 × 2), 6.85 (2H, s, C8, C9-H × 2), 6.73 (1H, s, C3-H). MS *m/z* (Rel. Int. %): 327 (M^+, 7.1), 326 (M^+-1, 3.8), 312 (M^+-15, 12.6), 296 (M^+-31, 17.6), 297 (M^+-30, 6), 283 (3.8), 282 (6.6), 281 (14.8), 280 (11.5), 279 (3.3), 267 (0.4), 266 (8.3).

Acetylation of sanjoinine-Ib (norisocorydine)

Sanjoinine-Ib (20 mg) was acetylated with Ac_2O and pyridine at RT overnight. After removal of reagents the residue was purified by pipette column (silicagel, $CHCl_3$-EtOAc-MeOH 50:10:1) to give a pure acetate (19 mg). mp 118 °C, IR λ_{max} cm^{-1} (KBr) 1630 (N-$COCH_3$), 1740 ($OCOCH_3$). ^1H NMR ($CDCl_3$, δ ppm): 2.16 (3H, s, N-$COCH_3$), 2.25 (3H, s, C11-$OCOCH_3$), 3.13-2.54 (6H, C4, C5, C7-CH_2 × 3), 3.44 (3H, s, C1-OCH_3), 3.85 (3H, s, C10-OCH_3), 3.88 (3H, s, C2-OCH_3), 4.85 (1H, br, C6a-H), 6.72 (1H, s, C3-H), 6.92 (1H, d, J = 8.2 Hz, C9-H), 7.16 (1H, d, J = 8.4 Hz, C8-H). MS *m/z* (Rel. Int. %): 411 (M^+, 216), 396 (M^+-15, 0.1), 380 (M^+-31, 0.1), 354 (0.5), 353 (0.3), 352 (M^+-59, 0.9), 340 (M^+-71, 0.3), 339 (M^+-72, 1.2), 337 (0.3), 310 (11.4), 297 (10.9).

Isolation of sanjoinine-K (coclaurine) and caaverine

Fr. 6 (1.67g) and fr. 7 (1.9g) were chromatographed over silicagel with $CHCl_3$-MeOH (5:1) and gave two fractions positive in Dragendorff's reagent and Pauly's reagent. Two fractions showed Rf. 0.3 and Rf. 0.25 in $CHCl_3$-MeOH-H_2O (3:1:0.1). Rf. 0.3 fraction yielded sanjoinine-K (840 mg, 1.4×10^{-3}% yield). Rf. 0.25 band gave caaverine (11 mg, 6.8×10^{-5}% yield) after preparative TLC purification ($CHCl_3$-MeOH-H_2O (3:1:0.1).

Sanjoinine-K: mp 159-161 °C (plates from acetone), $[\alpha]_D^{22}$ + 35° (C = 0.15, MeOH), ^1H NMR (DMSO-d_6, δ ppm): 3.3-2.8 (6H, CH2 × 3), 3.74 (3H, s, C6-OCH_3), 4.47 (1H, t, C1-H), 6.55 (1H, s, C8-H), 6.73 (1H, s, C5-H), 6.74 (2H, d, J = 8.4 Hz, C3′, C5′-H × 2), 7.13 (2H, d, J = 8.4 Hz, C2′, C6′-H × 2), 8.90 (1H, s, OH), 9.41 (1H, s, OH). MS *m/z* (Rel. Int. %): 285 (M^+, 0.1), 284 (M^+-1, 0.2), 192 (0.2), 178 (100), 177 (2.3), 163 (21.1), 162 (2.3), 148 (1.2), 134 (5.7), 107 (5.8).

Caaverine: mp 204 °C, $[\alpha]_D^{26}$-80° (c = 0.5, MeOH), ^1H NMR (CD_3OD, δ ppm): 3.15-2.8 (6H, m, C4, C5, C7-CH_2 × 3), 3.72 (3H, s, C2-OCH_3), 6.79 (1H, s, C3-H), 7.45-7.38 (3H, m, C8, C9, C10-H × 3), 8.44 (1H, m, C11-H). MS *m/z* (Rel. Int. %): 267 (M^+), 266 (M^+-1, 2.1), 251 (5.6), 250 (18.4), 219 (2.1), 235 (5.6), 178 (17.1).

Acetylation of caaverine

Caaverine (5mg) was acetylated with Ac_2O and pyridine at RT overnight. The excess reagents were removed by N_2 purgeing and the residue was purified by preparative TLC (silicagel, $CHCl_3$-MeOH 10:1) to give an acetate (4 mg). ^1H NMR ($CDCl_3$, δ ppm): 2.19 (3H, s, N-$COCH_3$), 2.36 (3H, s, C1-$OCOCH_3$), 3.58 (3H, s, C2-OCH_3), 6.86 (1H, s, C3-H), 7.35-7.25 (3H, m, C8, C9, 10-H × 3), 8.37 (1H, m, C11-H). MS *m/z* (Rel. Int. %) 351 (M^+, 6.3), 279 (M^+-72, 4.8), 250 (28.6), 238 (21.4), 237 (32.5), 236 (2.4), 178, 165.

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