Pure & Appl. Chem., Vol. 61, No. 3, pp. 443–448, 1989.
Printed in Great Britain.

Chemical and pharmacological studies on sedative cyclopeptide alkaloids in some Rhamnaceae plants

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Abstract - With reference to the clinical importance of "Sanjoin", the seeds of Zizyphus vulgaris var. spinosus in oriental medicine as one of the reliable medicinal agents for hypnotic or tranquilizing efficacy, phytochemical studies and some pharmacological studies on the alkaloid components in the Zizyphus plants were conducted. Several 14-membered cyclopeptide alkaloids were found as the major active principles for the sedative activity of the drug. The scientific basis for the roasting of Sanjoin before its use as a traditional drug was established by our molecular pharmacological studies on these cyclopeptide alkaloids.

INTRODUCTION

Sanjoin, the seeds of Zizyphus vulgaris Lamark var. spinosus Bunge(Rhamnaceae) has been frequently used in the oriental traditional medicine as an important and reliable hypnotic or sedative agent for the treatment of insomnia (ref. 1-3). Based on the descriptions found in the old Chinese Materia Medica, oriental herbal medicine doctors customarily use the drug after it has been roasted on hot plate at high temperature. In earlier studies on the pharmacological aspects of this drug, hypnotic (ref. 5), tranquilizing (ref. 6), sedative (ref. 7-10), analgesic (ref. 7), antiinflammatory (ref. 7), antiarrhythmic (ref. 11) and hypotensive (ref. 12) activities have been described. Some phytochemical papers describe the isolation of saponin components (ref. 10), Jujuboside A and B and flavonoid components (ref. 9,10) such as Swertisin, Spinosin, 6"'-sinapoylspinosin, 6"'-feruloylspinosin and p-coumaroylspinosin as the active principles for the sedative activity. The effective doses of the isolated flavonoid and saponins for the sedative activity seemed to be somewhat higher than that expected for the pure effective components (ref. 10). There were some papers reporting the major tranquilizing activity of alkaloidal fraction (ref. 6), however there were no mention on the isolation of the alkaloids. While Daechu, the fruits of another related plant, Zizyphus jujuba Miller var. inermis Rehder is used in oriental medicinal prescription without any pharmacological basis. In this connection, we have undertaken to study these two Rhamnaceae plants which resulted in the isolation of a number of alkaloid components from Sanjoin and fruit and bark of Daechu tree (ref. 13-17). During the purification of the compounds, the hypnotic or sedative activity

TABLE 1. Fractionation scheme and sedative activity of fractions of Sanjoin

Sanjoin (5.5 kg)
↓
Benzene extract (1865 g) ⟶ Alkaloidal fraction (0.65 g)
↓
Methanol extract (440 g) ⟶ Ether fraction (180 g)
↓ ↓
Butanol fraction (46 g) Alkaloidal fraction (0.52 g)
↓
Water fraction (213 g)

Fraction	Sleeping Time	
	Control	Sample
Methanol extract (1.0 g/kg)	27.7 ± 7.6	46.5 ± 17.3
C_6H_6 alkaloid fraction (50 mg/kg)	23.6 ± 11.8	29.2 ± 11.7
Ether fraction (0.5 g/kg)	27.7 ± 7.6	30.3 ± 11.0
Butanol fraction (0.5 g/kg)	28.8 ± 16.3	41.2 ± 15.4
Water fraction (0.5 g/kg)	28.8 ± 16.3	27.5 ± 14.3

Samples were orally administered 60 min. before hexobarbital-Na(50 mg/kg) i.p. injection. sleeping time in min., n=6-7, mean ± S.E.

was monitored by measuring the prolongation of hexobarbital induced sleeping time of mice. As shown in Table 1, benzene soluble alkaloidal fraction showed sedative activity at very low doses. Based on this pharmacological data we started to isolate the alkaloids by column chromatography.

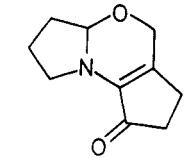
CHEMISTRY

With combined flash column chromatography and preparative thin layer chromatography fourteen alkaloids (Table 2) were isolated in crystalline state from Sanjoin, five alkaloids from Daechu (Table 3) and twelve alkaloids from the Stem bark of Daechu tree (Table 4).

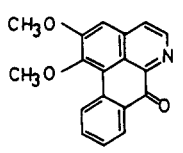
The alkaloids were labeled as Sanjoinine-A, B, C, etc. Daechualkaloid-A, C, E, etc. and Daechuine-S1, S2 etc. in the order of increasing polarity. The isolation yields were highly varied ranging from 1.4×10^{-3} % to 5×10^{-6}%. The chemical structures of all those alkaloids were established in some cases by combination of chemical correlation methods and spectral analyses.

As shown in Table 5, Sanjoinine-A, B, D, F, G1 and Sanjoinenine isolated from Sanjoin were identified as cyclopeptide alkaloids and Sanjoinine-G2 as open chain peptide alkaloid which could also be obtained by the ring opening of Sanjoinine-A by OsO_4-$NaJO_4$ treatment (ref. 18). Sanjoinine-D could also be obtained from Sanjoinine-G1 by the methylation of the later in the presence of CH_2N_2/BF_3.

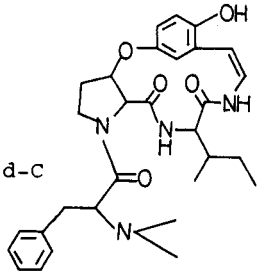
Other Sanjoinine alkaloids were identified as Nuciferine, Nornuciferine, Norisocorydine, N-methylasimilobine and Caaverine which are included as alkaloids of aporphine series. Sanjoinine-K was identified as Coclaurine, a benzylisoquinoline alkaloid. A new quarternary aporphine alkaloid was isolated from the butanol fraction and named Ziziphusine. From the Daechu, five alkaloids were isolated in crystalline state. Occurrence of Zizyphusine was common to both Sanjoin and Daechu. Daechucyclopeptide-1 was a new cyclopeptide alkaloid with 13-membered ring structure.



Daechualkaloid-A



Daechualkaloid-C



Daechucyclopeptide-I

Fig. 1. Alkaloids from Daechu

Daechualkaloid-C and E were identified as Lysicamine and Nornuciferine respectively, while Daechualkaloid-A was found to be a new alkaloid with a novel tricyclic pyrrolidine skeleton (ref. 17). From the stem bark of Daechu tree, twelve cyclopeptide alkaloids were isolated and designated as Daechuin-S1, S2 etc. The structure were fully assigned by spectral analyses and comparison of spectral data with those of Sanjoin alkaloids.

Of the twelve alkaloids from bark of Daechu tree, four were 14-membered cyclopeptide alkaloids and the rest were 13-membered cyclopeptide alkaloids. In all, seven of them were new alkaloids and the others were known compounds found in other plants. In summary, the major alkaloid components of Sanjoin and Daechu were found to be Sanjoinine-A (14-membered cyclopeptide alkaloid, Frangufoline), Sanjoinine-K (benzylisoquinoline, coclaurine), and Ziziphusine (quarternary aporphine alkaloid).

TABLE 2. Alkaloids isolated from Sanjoin

Compound	mp (°C)	$[\alpha]_D$(deg)	Yield (%)
Sanjoinine-A (Frangufoline)	249	-316	6×10^{-3}
Sanjoinine-B (New)	212-4	-	5.5×10^{-6}
Sanjoinine-D (New)	256-8	-53.6	4×10^{-5}
Sanjoinine-F (New)	228	-215	1.3×10^{-4}
Sanjoinine-G1 (New)	236-8	-68.6	3.5×10^{-5}
Sanjoinine-G2 (New)	182	-79.2	1.6×10^{-4}
Sanjoinenine (New)	281-2	-272.5	2.2×10^{-4}
Sanjoinine-E (Nuciferine)	166	-146.2	2.7×10^{-5}
Sanjoinine-I_a (Nornuciferine)	155-7	-140	1.2×10^{-4}
Sanjoinine-I_b (Norisocorydine)	184		8.7×10^{-5}
Sanjoinine-K (+ Coclaurine)	159-161	+35	1.4×10^{-3}
N-methylasimilobine	193-5	-204	5×10^{-6}
Caaverine	204	-80	6.8×10^{-5}
Zizyphusine (New)	214-216	+317	6.2×10^{-3}

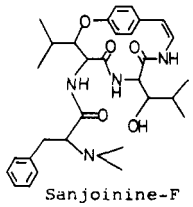
TABLE 3. Alkaloids isolated from Daechu, the fruit of Daechu tree

Compound	mp(°C)	Yield (%)
Daechualkaloid-A	52	1.3×10^{-3}
Daechualkaloid-C (Lysicamine)	212	2.4×10^{-4}
Daechualkaloid-E (Nornuciferine)	204	5.1×10^{-4}
Daechucyclopeptide-I	114	4.1×10^{-5}
Zizyphusine	214-5	6.2×10^{-4}

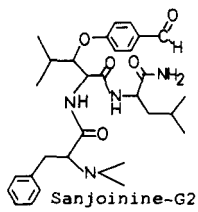
TABLE 4. Alkaloids from the Daechu tree

Compound	mp(°C)	$[\alpha]_D$(deg)	Yield (%)
Daechuine-S1	250	-316	6.3×10^{-5}
Daechuine-S2	238-42	-118.6	2.6×10^{-4}
Daechuine-S3	192-94	-440	5.9×10^{-4}
Daechuine-S4	239-41	-297	3.4×10^{-4}
Daechuine-S5	233-35	-421.3	2.8×10^{-5}
Daechuine-S6	192	-393.5	6.2×10^{-4}
Daechuine-S7	158	-648.3	1.4×10^{-4}
Daechuine-S8-1	185-88	-218.2	1.2×10^{-4}
Daechuine-S9	115	-481	1.7×10^{-4}
Daechuine-S10	126-28	-381.5	6.9×10^{-4}
Daechuine-S26	114	--	6.5×10^{-5}
Daechuine-S27	226-28	-386	4.8×10^{-4}

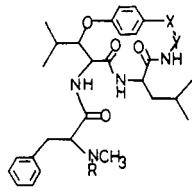
TABLE 5. Cyclopeptide alkaloids from Sanjoin

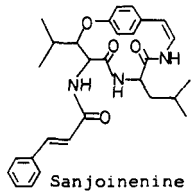


Sanjoinine-F



Sanjoinine-G2

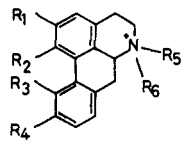


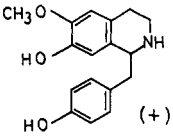


Sanjoinenine

Compound		R	X-Y
Sanjoinine-A	(Frangufoline)	CH_3	CH=CH
Sanjoinine-B	(New)	H	CH=CH
Sanjoinine-D	(New)	CH_3	$CH(OCH_3)-CH_2$
Sanjoinine-G1	(New)	CH_3	$CH(OH)-CH_2$

TABLE 6. Aporphine alkaloids from Sanjoin



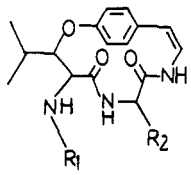


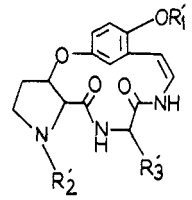
(+)-Coclaurine

R_1,R_2,R_5= CH_3	R_3,R_4,R_6= H	:Nuciferine
R_1,R_3,R_4,R_6= H	R_2,R_5= CH	:N-methylasimilobine
R_1,R_2= CH_3	R_3,R_4,R_5,R_6= H	:Nornuciferine
R_1,R_2,R_4= CH_3	R_3,R_5,R_6= H	:Norisocorydine
R_1= CH_3	R_2,R_3,R_4,R_5,R_6= H	:Caaverine
R_1,R_2= H	R_3,R_4,R_5,R_6= CH_3	:Zizyphusine

TABLE 7. Cyclopeptide alkaloids from stem bark of Daechu tree

Compound		R_1	R_2
Daechuine-S1	(Frangufoline)	$N(CH_3)_2$Phe-	$(CH_3)_2CHCH_2$-
Daechuine-S2	(Frangulanine)	$N(CH_3)_2$Ile-	$(CH_3)_2CHCH_2$-
Daechuine-S4	(Franganine)	$N(CH_3)_2$Leu-	$(CH_3)_2CHCH_2$-
Daechuine-S5	(New)	$N(CH_3)_2$Val-	$(CH_3)_2CHCH_2$-





Compound		R_1'	R_2'	R_3'
Daechuine-S3	(New)	CH_3	$N(CH_3)_2$Ile-Ile-	$CH_3CH_2CH(CH_3)$-
Daechuine-S6	(New)	CH_3	$N(CH_3)_2$Phe-	$CH_3CH_2CH(CH_3)$-
Daechuine-S7	(New)	CH_3	$N(CH_3)_2$Leu-	$(CH_3)_2CHCH_2$-
Daechuine-S8-1	(New)	CH_3	$N(CH_3)_2$Leu-Leu-	$(CH_3)_2CHCH_2$-
Daechuine-S9	(Mucronin-D)	CH_3	$N(CH_3)_2$Phe-Leu-	$CH_3CH_2CH(CH_3)$-
Daechuine-S10	(New)	CH_3	$N(CH_3)_2$Try-	$CH_3CH_2CH(CH_3)$-
Daechuine-S26	(New)	H	$N(CH_3)_2$Phe-	$CH_3CH_2CH(CH_3)$-
Daechuine-S27	(Nummularin-B)	CH_3	$NH(CH_3)$Ala-Val-	Benzyl

SEDATIVE ACTIVITY

The alkaloids were isolated from the Sanjoin extract with monitoring the sedative activity by measuring the hexobarbital induced sleeping time.
As shown in Table 1, oral administration of methanol extract (1.0 g/Kg) prolonged the hexobarbital induced sleeping time by more than 67% compared to the control group. From 60Kg of Sanjoin we could obtain 20g of alkaloidal fraction and 450g of butanol fraction. Butanol fraction showed more potent sedative activity. However, isolation of alkaloids from ether soluble alkaloidal fraction was successful. As shown in Table 2, Sanjoinine-A was the major alkaloid from Sanjoin.

TABLE 8. Effect of alkaloids from Sanjoin on hexobarbital induced sleeping time

	Cyclopeptide	Aporphine		Tetrahydrobenzylisoquinoline
	Sanjoinine-A	Nuciferine	Zizyphusine	Coclaurine
Control	16.3±9.8	27.8±10.4	20.6±2.1	20.6±2.1
3 mg/kg	26.1±13.1	33.3±13.8		
10 mg/kg	30.6±19	52.4±17.5	20.0±5.9	16.8±4.3
33 mg/kg			22.2±6.9	16.1±8.0

Samples were orally administered 1 hr before hexobarbital-Na (50 mg/kg) i.p. injection. sleeping time in min., n=6-7, mean ± S.E.

As shown in Table 8, Sanjoinine-A and Nuciferine showed strong sedative activity whereas Zizyphusine and Coclaurine didn't. Nuciferine have been already reported as having major tranqulizing nature(ref. 19). The sedative activity of Sanjoinine-A at dose of 3 mg/Kg was potent enough to establish such cyclopeptide alkaloids can be effective components in Sanjoin and this was the first finding of sedative activity in cyclopeptide alkaloids. Actually all these alkaloids exist as a mixture in a certain ratio in Sanjoin, so some drug interactions such as additivity, synergistic or counteracting interaction could be postulated. In order to clarify these possibilities, Sanjoinine-A was co-administered with Nuciferine and Coclaurine respectively.

TABLE 9. Effect of co-administration of Sanjoinine-A and Nuciferine on hexobarbital induced sleeping time

Control	Sanjoinine-A 1 mg/kg	Sanjoinine-A 1 mg/kg + Nuciferine 2.5 mg/kg	Sanjoinine-A 1 mg/kg + Nuciferine 5 mg/kg	Nuciferine 5 mg/kg
32.1 ± 23.8	50.8 ± 11.0	46.1 ± 11.3	97.5 ± 31.0	83.3 ± 19.5

Samples were administered i.p. 30 min. before hexobarbital-Na (50 mg/kg) i.p. injection. sleeping time in min., n=7, mean ± S.E.

TABLE 10. Effect of co-administration of Sanjoinine-A and Coclaurine on hexobarbital induced sleeping time

Control	Sanjoinine-A 1 mg/kg	Sanjoinine-A 1 mg/kg + Coclaurine 10 mg/kg	Coclaurine 10 mg/kg
34.1 ± 11.5	47.8 ± 17.5	50.7 ± 11.4	38.6 ± 13.8

Samples were administered i.p. 30 min. before hexobarbital -Na (50 mg/kg) i.p. injection. sleeping time in min., n=7, mean ± S.E.

Table 9 shows that there is additivity between Sanjoinine-A and Nuciferine while Table 10 indicates that Coclaurine does not enhance the sedative activity of Sanjoinine-A. Zizyphusine, a quarternary aporphine alkaloid isolated as a major alkaloid component from butanol fraction, showed no sedative activity. As a result, the potent sedative activity of butanol fraction could not be explained by the high content of Zizyphusine. Some paper describes the sedative activity of flavonoids or saponins which constitute the major part of butanol fraction (ref. 10). In fact the butanol fraction contains also small amount of aporphine alkaloids such as Caaverine and N-methylasimilobine and Norisocorydine etc. as minor components impurity which are very difficult to seperate by solvent partition due to the formation of salt with flavonoids (ref. 16). It is highly probable that some part of the sedative activity of the butanol fraction may be contributed by the presence of these minor alkaloids.

HEAT INDUCED EPIMERIZATION OF SANJOININE-A

Old Chinese Materia Medica (Ref. 4) described that the roasting of Sanjoin potentiate its hypnotic activity. In practice Chinese medicine doctors in Korea use the roasted Sanjoin for the hypnotic purposes. In order to check whether the classical record on the heat treatment of Sanjoin appeared in old Chinese Materia Medica bears any relevance on the pharmacological nature of Sanjoin alkaloid, the Sanjoin alkaloids were subjected to high temperature treatment. When we treated the aporphine alkaloids such as Nuciferine and Nornuciferine, we could obtain dehydrogenated product lysicamine in all cases. This heat induced transformation was a irreversible reaction. However, when Sanjoinine-A, the cyclopeptide alkaloid was treated at high temperature of 220°C in an oil bath for 15 minutes we could obtain heat-induced artefact Sanjoinine-Ahl which was interconvertible with Sanjoinine-A at the same temperature (ref. 14, 16).

TABLE 11. Effect of Sanjoinine-A and Sanjoinine-Ahl on hexobarbital induced sleeping time.

		Sanjoinine-A			Sanjoinine-Ahl	
Control	1 mg	3 mg	10 mg/kg	1 mg	3 mg	10 mg/kg
Exp.1 18.3±8	26.1±7.1	30.2±7.2		32.8±12.4	33.2±12.2	
Exp.2 11.5±4.1		25.8±18.5	45.1±11.9		39.3±16.1	46.0±23.9

Samples were administered i.p. 30 min. before hexobarbital-Na (50 mg/kg) i.p. injection. sleeping time in min., n=6-7, mean ± S.E.

TABLE 12. Effect of lysicamine and nornuciferine on hexobarbital induced time

Control	Lysicamine		Nornuciferine	
	1 mg/kg	3 mg/kg	3 mg/kg	
29.5±11.1	34.3±18.5	44.7±15.4	46.4±17.8	

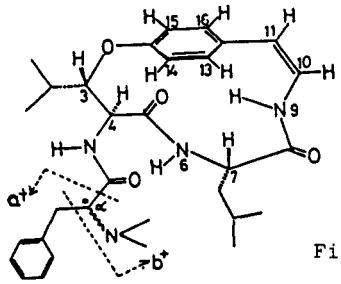
Samples in 1% CMC were administered i.p. 30 min. before hexobarbital-Na(50 mg/kg) i.p. injection. sleeping time in min., n=7, mean ± S.E.,

Table 11 showes the comparison of sedative data between Nornuciferine and Lysicamine which was produced as artefact from Nornuciferine by high temperature treatment and the sedative activity of Lysicamine is not enhanced (ref. 13).
Therefore the prescription in the classical record on Sanjoin could be verified by the modern molecular pharmacological studies on the cyclopeptide alkaloid component. We tried to elucidate the complete chemical mechanism of interconversion of Sanjoinine-A and Sanjoinine -Ahl by our chemical and spectrometric studies on the stereochemical structures of Sanjoinine-A and Sanjoinine-Ahl. Sanjoinine-A and Sanjoinine-Ahl were interconvertible each other at high temperature(220 °C) but not at low temperature treatment such as by boiling in a water bath. The mass spectra of these two compounds was completely superimposable. Furthermore the PMR spectra was also similar with some difference change in the chemical shifts of some methyl signals. Therefore no covalent bond cleavage was expected during the interconversion between two isomers. Two mechanisms for the interconversion between the two substances at high temperature were postulated,

1) conformational isomerization arising from the rigid 14-membered ring conformation
2) stereochemical isomerization arising from four chiral carbons.

To check the possibility for the conformational isomerization, the 14-membered ring of both Sanjoinine-A and Sanjoinine-Ahl were opened by oxidation of the olefin bond using OsO_4 - $NaJO_4$ oxidation procedure. The products resulted from ring opening reaction of both Sanjoinine-A and Sanjoinine-Ahl were not identical. That suggested there was no conformational isomerization but the stereochemical isomerization in certain chiral carbons. It is a well established fact that amino acid is racemized at high temperature due to α-proton mobilization via enol-tautomerization (ref. 20). In order to verify whether this mechanism of interconversion between two compounds operative, we prepared deuterated Sanjoinine-Ahl by heating Sanjoinine-A in the presence of deuterium oxide (ref. 14). The resulting deuterated Sanjoinine-Ahl was obtained after removing the exchangeable deuterium of amide group by back-exchange treatment and followed by chromatographic purification. The mass spectra of deuterated Sanjoinine-Ahl gave typical fragment ions in which M+, a+ and b+ showed one mass unit upward shift, suggesting the mobilization of α-proton of N,N-dimethylphenylalanine moiety. The deuterium exchange in α-proton was also confirmed by the facts that the PMR spectra of deuterated Sanjoinine-Ahl showed the disappearance of α-proton peaks of N,N-dimethylphenylalanine moiety and two β-protons as AB-quartet instead of multiplet. The CMR spectra supported the deuteration of α-proton in N,N-dimethylphenylalanine moiety by the disappearance of α-carbon peak at 70 ppm also. These facts suggested us conclusively that the interconversion between Sanjoinine-A and Sanjoinine-Ahl was arised from the epimerization of the chiral carbon in N,N-dimethylphenylalanine side chain, and that Sanjoinine-A and Sanjoinine-Ahl have no

difference in the stereostructure of fourteen membered cyclic-peptide moiety also. And we applied the Hudson's rule (ref. 21) for the analysis of absolute configuration of N,N-dimethylphenylalanine, which gave the final answer as being l-series for Sanjoinine A and d-series for Sanjoinine Ahl. In order to determine the stereostructure of the ring bound amino acids, Sanjoinine A was hydrolyzed and the hydrolysate was treated to produce l-menthol ester of amino acid (ref. 22). By the GLC analyses of this diastereoisomeric derivatives, we determined the leucine moiety in ring structure as l-series. The stereostructure of the two chiral carbon in oxyleucine moiety could not be determined by this method, since the oxyleucine was completely destroyed by acid hydrolysis.



heat
(1) ⇌ (2)
α=(S)-L- (R)-D-

Fig. 2. Structure of Sanjoinine-A(1) and Sanjoinine-Ah1(2)

The stereostructure of β-oxyleucine could be determined as l-erythro series by molecular model construction considering the dihedral angle obtained by analysis of proton-proton coupling constants and NOE-data. NOE-data suggested that the Sanjoinine-Ahl had slightly distorted cyclic structure due to the inversion of chiral carbon of N,N-dimethylphenylalanine moiety (ref. 22).

SUMMARY

Several 14-membered cyclopeptide alkaloids and some aporphine alkaloids were isolated as the active principles for the sedative or hypnotic activity of "Sanjoin", the seed of Zizyphus vulgaris. The ethnopharmacological aspect in the application of Sanjoin, i.e., roasting of the Sanjoin to enhance the hypnotic activity was reflected in pharmacological and stereochemical properties of its cyclopeptide alkaloids as the effective components.

Acknowledgements

The authors are grateful to Korea Science and Engineering Foundation for the support of research grants.

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