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THE ALKALOIDS OF *STEPHANIA SASAKII*: STRUCTURE OF FIVE NEW ALKALOIDS*

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Key Word Index *Stephania sasakii*; Menispermaceae; dehydrocrebanine; 4,5-dioxodehydrocrebanine; bisaknadinine; stesakine; dehydrostesakine.

Abstract—Five new alkaloids, dehydrocrebanine, 4,5-dioxodehydrocrebanine, stesakine, dehydrostesakine, bisaknadinine and four known alkaloids, lirodenine, lanuginosine, l-tetrahydropalmatine, *d*-isocorydine with a few alkaloids of unknown structure were newly isolated from *Stephania sasakii*. The structures of the new alkaloids were determined from spectral data and chemical evidence.

INTRODUCTION

In previous papers, we have reported the isolation and structural determination of several alkaloids in *Stephania sasakii* Hayata (Menispermaceae) from Formosa [1–4]. Here we report on the tertiary base fraction from this plant which gave five new alkaloids and four known alkaloids. The structure of the five new alkaloids were established by a combination of spectroscopic and chemical methods.

RESULTS AND DISCUSSION

Thirteen alkaloids previously unreported from *S. sasakii* were isolated and purified as described in the Experimental. These include four unknowns (bases A, B, C and D) and five new compounds (**1**, **3**–**5**, **11**) (Table 1). The structures of the other four known alkaloids, liriodenine (**6**), lanuginosine (**7**), l-tetrahydropalmatine (**12**) and *d*-isocorydine (**13**), were fully identified by direct comparison (mmp, IR, UV, MS, ^{1}H NMR and TLC) with authentic samples and all gave correct elemental analyses.

Dehydrocrebanine (**4**) had a mp 151–152° and its composition ($C_{20}H_{19}NO_4$) was determined by MS and elemental analyses. The UV and MS spectra show that it is a dehydroaporphine-type alkaloid. The ^{1}H NMR showed the presence of two methoxyl, an *N*-methyl and one methylenedioxy groups with four aromatic protons: in the aromatic protons, two signals at δ 6.99 (*d*, J = 9.0 Hz) and 8.67 (*d*, J = 9.0 Hz) were due to *ortho* hydrogens. These facts suggested that **4** was a dehydro derivative of crebanine (**2**), the main alkaloid of *S. sasakii*. Evidence for the structure of **4** was established by dehydrogenation of **2** with iodine in dioxane [5] which gave a dehydro derivative identified with natural **4**.

4,5-Dioxodehydrocrebanine (**5**) had mp 278–280° and its MS and elemental analyses established the formula as $C_{20}H_{15}NO_6$. The UV spectrum indicated a highly conjugated system in comparison with that of **4**, and the IR showed a conjugated ketone or a six-membered lactam. The ^{1}H NMR showed the presence of two methoxyl, one *N*-methyl and one methylenedioxy groups and four aromatic protons. But, in comparison with the ^{1}H NMR spectra of **2** and **4**, the signals of the *N*-methyl group and two aromatic protons at δ 7.55 and 7.83 are unusually low-shielded. These facts suggested that the B-ring of the aporphine-type alkaloid was highly strained as expected for 4,5-dioxodehydroaporphine-type alkaloids of type **2** [6]. Recently, Kunitomo *et al.* [7] reported that air oxidation of dehydroaporphine with an alkali catalyst gave 4,5-dioxodehydroaporphine along with 7-oxoaporphine and *N*-methylaristolactam type-substances in low yield. This reaction with dehydrocrebanine (**4**) afforded the corresponding 4,5-dioxodehydrocrebanine (**5**), which was identified with the natural product, and the corresponding 7-oxoaporphine (**8**), an *N*-methyl-aristolactam-type compound (**9**).

Stesakine (**1**) (mp 188–190°; $[\alpha]_D$ − 78.7° ($CHCl_3$)), had a molecular formula $C_{19}H_{19}NO_4$. Its UV spectrum is consistent with the formula for **2** [8], and it exhibits a bathochromic shift in alkaline solution. Its IR spectrum shows the presence of a hydroxyl group. Its ^{1}H NMR spectrum shows the presence of one methoxyl, one *N*-methyl and one methylenedioxy groups, three aromatic protons and a hydroxyl proton at δ 4.55. On *O*-methylation of this base with diazomethane crebanine (**2**)

* Part XI in the series "The Alkaloids of *Stephania sasakii*". For Part X see ref. [1]. This paper constitutes Part 268 in the series "Studies on the Alkaloids of Menispermaceous Plants". For Part 267 see Matsui, M., Uchida, M., Usui, I., Saionji, Y., Murata, H. and Watanabe, Y. (1979) *Phytochemistry* **18**, 1087. Part of the contents was reported by rapid publication: Kunitomo, J., Oshikata, M., Murakami, Y. and Shingu, T. (1980) *Heterocycles* **14**, 175.

Table 1. Additional alkaloids of *Stephania sasakii*

Compound	mp (°)	$[\alpha]_D$ (solvent)	Yield (mg)*
Non-phenolic bases			
Dehydrocrebanine (**4**)	151–152	-	704
4,5-Dioxodehydrocrebanine (**5**)	278 280		26
Liriodenine (**6**)	273 275	- -	31
Lanuginosine (**7**)	>300	---	22
1-Tetrahydropalmatine (**12**)	141–143	−276.1° (EtOH)	1440
Base A	191–192	−90.2° ($CHCl_3$)	62
Base B	192 194	−2.4° ($CHCl_3$)	170
Base C	183–185	−33.2° ($CHCl_3$)	76
Phenolic bases			
Stesakine (**1**)	188–190	−78.7° ($CHCl_3$)	16
Dehydrostesakine (**3**)	201 203	--	37
Bisaknadinine (**11**)	198-200	−253.3° ($CHCl_3$)	30
d-Isocorydine (**13**)	184 185	+191.9° ($CHCl_3$)	10
Base D	127 128	−32.1° ($CHCl_3$)	10

* From 6.9 kg of dried material.

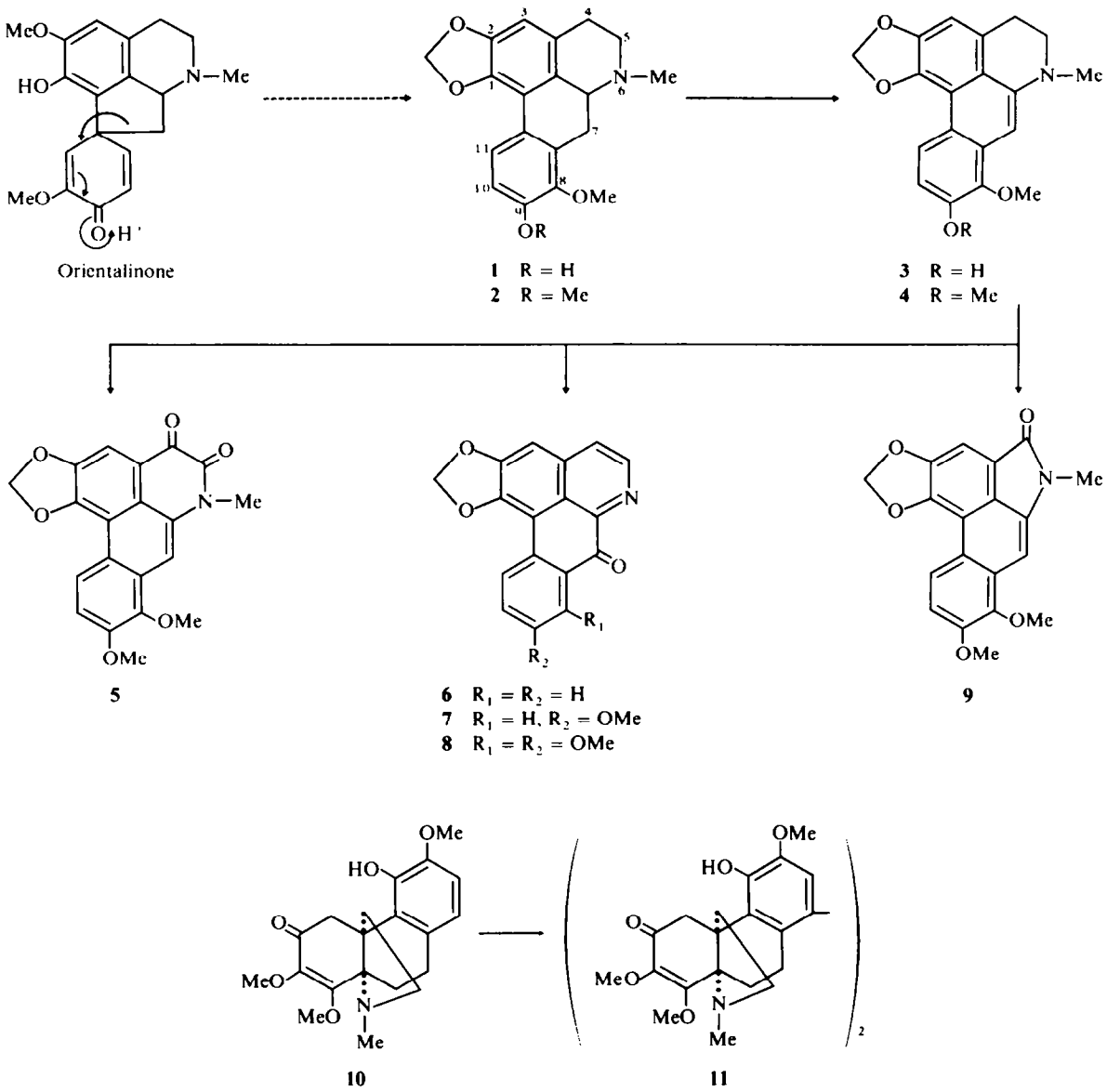
is formed [2]. For determination of the position of the phenolic function, deuterium exchange of the aromatic proton was carried out. The doublet signal of the C-11 aromatic proton at δ 7.81 changed into a singlet, and the signal of the C-10 aromatic proton at δ 6.93 disappeared. It follows that the phenolic function must be at C-9. Therefore the structure of this alkaloid was determined as **1** and named stesakine.

Dehydrostesakine (**3**) had mp 201–203° and the IR spectrum showed a hydroxy group at 3500 cm^{-1}. Elemental analyses and MS established the formula as $C_{19}H_{17}NO_4$. The UV spectrum was quite similar to **4** except a bathochromic shift was noted upon the addition of alkali. The ^1H NMR spectrum revealed the presence of one methoxyl, one *N*-methyl, and one methylenedioxy groups, four aromatic protons and a hydroxy proton at δ 5.88. On *O*-methylation of this base with diazomethane it yielded an *O*-methyl derivative identical with **4**. These facts suggested that this base is an *O*-demethyl derivative of **4**. In order to determine the position of the methoxyl group in **3**, nuclear Overhauser effect (NOE) and internuclear double resonance (INDOR) were applied. In the INDOR determination of **3**, no peak was observed in reference to the aromatic proton of C-10 at δ 6.99 by monitoring the signal of the methoxyl at δ 3.96, but it was observed in regard to the hydroxyl group at δ 5.88. These facts suggest that the position of the methoxyl group was at C-8. This observation indicates the presence of NOE, that is, the signal area of the aromatic proton at δ 6.83 increases 9.8 or 15.8%, by monitoring the signal of the methoxyl group at δ 3.96 or the *N*-methyl group at δ 3.10, respectively. Consequently, the signal of the aromatic proton at δ 6.83 was in the C-7 position, and the structure of this base is concluded to be **3**.

The occurrence of stesakine (**1**) and dehydrostesakine (**3**) together with **2** strongly supports Battersby's assumption on the biogenesis of unusual 1,2,8,9-substituted aporphines. A dienone-phenol rearrangement of orientalinone must give **1** which was the assumed intermediate compound for the biogenesis of **2** from orientalinone [9].

Bisaknadinine (**11**) had mp 198–200°, $[\alpha]_D$ − 253.3° ($CHCl_3$) and shows a molecular ion peak at *m/e* 716.8 confirming the formula $C_{40}H_{48}N_2O_{10}$. Its UV, IR and ^1H NMR spectra data are very similar to those of aknadinine (**10**) [4] except the relative intensity of aromatic protons are reduced to one half in the ^1H NMR spectrum. These facts predicts that the dimer included a biphenyl moiety which was composed of two identical radicals lacking one aromatic proton from **10**. The bonding position of aromatic rings of biphenyl moiety in this base was determined as follows. By INDOR measurement of the base, a peak was observed with the methoxyl group at δ 3.83 by monitoring the signal of the aromatic proton at δ 6.57. In the presence of NOE, the signal area of the aromatic proton increased 16.8% by monitoring the signal of the methoxyl group. From the aforesaid INDOR and NOE data, the aromatic proton and methoxyl group must be *ortho*. Compound **11** was negative with 2,6-dichloroquinone-4-chlorimide (Gibb's reagent) in opposition to the monomer **10**. From these facts, the position of the biphenyl bond of this base was presumed in position C-1 of **10**. To determine the exact structure, including the absolute configuration of **11**, treatment of **10** with silver nitrate solution [10] gave a dimer, which was identified as natural **11** by direct comparison (mmp, ^1H NMR, TLC and specific rotation). From this reaction product, the diastereoisomer was also obtained in low yield. The absolute configuration concerning the mode of hindering free rotation around the biphenyl linkage was not determined only its ORD and CD data as reported by Brossi *et al.* [11]. This aspect must depend on future examination with X-ray diffraction. Bisaknadinine (**11**) constitutes the first example of a dimeric hasubanan-type alkaloid.

The exact structure of the unknown bases—and a few other bases which appeared on TLC (except those described above) have not been investigated so far.



EXPERIMENTAL

General procedure. All mps were uncorr. ^{1}H NMR spectra were determined with TMS as int. standard using a Varian A-60 or Hitachi R-22 (90 MHz). MS spectra were determined using a Hitachi RMU-6E: ion accelerating voltage 3.2 kV, chamber voltage 70 eV, total emission 80 μA, target current 72 μA, chamber temp. 220°. Specific rotation, ORD and CD were determined using a JASCO DIP-4 digital and model J-20, respectively.

Plant material. The ground stem and root of *Stephania sasakii* Hayata were collected in July 1969 in Orchid Island (Formosa)

Extraction and isolation of alkaloids. Air-dried and chopped ground stem and root (6.9 kg) were extracted with MeOH and non-phenolic (50.9 g) and phenolic bases (17.0 g) separated in the usual manner. Each fraction was column chromatographed in Si G monitored by TLC. In the case of a mixed alkaloid fraction, the fractions were purified by repeated column chromatography as described in a previous paper [2].

The non-phenolic bases. Dehydrocrebanine (**4**). Pale yellow needles (EtOH). UV λ_{max}^{EtOH} nm (log ε): 248 (sh, 4.36), 272 (4.77), 296 (sh, 4.17), 337 (4.15), 385 (3.49). ^{1}H NMR ($CDCl_3$): δ 3.10, 3.35 (4H, *m*, 2 CH_2), 3.12 (3H, *s*, NMe), 3.99 (6H, *s*, 2 OMe), 6.15 (2H, *s*, OCH_2O), 6.85 (2H, *s*, C-3 and C-7), 6.99 (1H, *d*, J = 9.0 Hz, C-10), 8.67 (1H, *d*, J = 9.0 Hz, C-11). MS *m/e* (rel. int.): 337 (M^+, 100), 322 (M^+ − Me, 70.6), 279 (322 − CH_3=NMe, 33.8), 338 (23.1). (Found: C, 70.99; H, 5.66; N, 4.01. Calc. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15%.) A direct comparison of the base with an authentic sample of **4**, dehydrogenation product of **2**, showed that both compounds were indistinguishable (mmp, TLC, superimposable IR and UV).

Preparation of **4** *by dehydrogenation of* **2**. **2** (100 mg) in dioxane (20 ml) was dehydrogenated with I_2 (90 mg) in dioxane (7 ml) containing suspended dry NaOAc (100 mg) by the method of ref. [5]. Recrystallization from EtOH afforded pale yellow needles of **4**, yield 54 mg, mp 152–153°.

4,5-Dioxodehydrocrebanine (**5**). Orange needles (EtOH). UV λ_{max}^{EtOH} nm (log ε): 220 (4.54), 244.5 (4.62), 308 (4.21), 321 (4.25), 435 (4.21). IR ($CHCl_3$) cm^{-1}: 1660 (conj. CO), 1593 (lactam). ^{1}H NMR ($CDCl_3$): δ 3.60 (3H, *s*, NMe), 4.06 (6H, *s*, 2 OMe), 6.30 (2H, *s*, OCH_2O), 7.24 (1H, *d*, J = 9.0 Hz, C-10), 7.55 (1H, *s*, C-3), 7.83

(1H, s, C-7), 8.47 (1H, d, J = 9.0 Hz, C-11). MS m/e (rel. int.): 365 (M^+, 100), 350 (M^+ − Me, 19.5), 377 (M^+ − CO, 17.5), 322 (350 − CO, 55.7), 305 (28.0), 294 (322 − CO, 11.1), 279 (294 − Me, 38.1), 277 (40.8), 264 (13.5). (Found: C, 66.28; H, 3.98; N, 3.67. Calc. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83%) These data correspond with those of an authentic sample of **5** (one of products of air oxidation of **4** with an alkali catalyst) and there was no mp depression in mmp determination.

Air oxidation of **4** *with alkali catalyst.* **4** (320 mg) in DMSO (15 ml) containing suspended *tert.*-BuOH (1.1 g) was stirred at room temp. for 20 hr according to the method described in ref. [7]. The reaction products were isolated by elution chromatography on Si G, and gave the following three compounds.

4,5-Dioxodehydrocrebanine (**5**): Orange needles (EtOH), mp 278 280°. UV λ_{max}^{EtOH} nm (log ε): 220 (4.50), 245 (4.63), 307 (4.21), 321 (4.25), 435 (4.09). IR ($CHCl_3$) cm^{-1}: 1660 (conj. CO), 1593 (lactam). ^1H NMR ($CDCl_3$): δ 3.57 (3H, s, NMe), 4.04, 4.06 (2 × 3H, s, 2 OMe), 6.31 (2H, s, OCH_2O), 7.23 (1H, d, J = 9.0 Hz, C-10), 7.46 (1H, s, C-3), 7.78 (1H, s, C-7), 8.43 (1H, d, J = 9.0 Hz, C-11). MS m/e (rel. int.): 365 (M^+, 100), 350 (M^+ − Me, 20.0), 337 (M^+ − CO, 28.8), 322 (350 − CO, 54.7), 294 (322 − CO, 9.5), 279 (394 − Me, 28.4). (Found: C, 65.93; H, 4.26; N, 3.52. Calc. for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83%)

1,2-Methylenedioxy-8,9-dimethoxy-7-oxodibenzo[de,g]quinoline (**8**): Orange prisms (EtOH), mp 265–269 . UV λ_{max}^{EtOH} nm (log ε): 249 (4.49), 276 (4.40), 380 (3.82), 440 (4.21). IR ($CHCl_3$) cm^{-1}: 1660 (conj. CO). ^1H NMR (CF_3COOD): δ 4.09 (3H, s, OMe), 4.17 (3H, s, OMe), 6.60 (2H, s, OCH_2O), 7.50 (1H, s, C-3), 7.69 (1H, d, J = 9.0 Hz, C-10), 8.40 (1H, d, J = 6.0 Hz, C-4), 8.70 (1H, d, J = 6.0 Hz, C-5), 8.72 (1H, d, J = 9.0 Hz, C-11). MS m/e (rel. int.): 335 (M^+, 83.9), 320 (M^+ − Me, 16.8), 307 (M^+ − CO, 10.5), 305 (M^+ − OCH_2, 13.4), 304 (21.8), 275 (53.6). (Found: C, 68.18; H, 3.81; N, 4.18. Calc. for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18%)

N-Methyl-1,2-methylenedioxy-8,9-dimethoxydibenzo [cd, f]indol-4-one (**9**): Yellow needles (Me_2CO), mp. 279-281 . UV λ_{max}^{EtOH} nm (log ε): 213 (4.48), 245 (4.60), 279 (sh, 4.51), 290 (4.62), 356 (4.00), 374 (3.94), 396 (3.88). IR ($CHCl_3$) cm^{-1}: 1685, 1650 (conj. CO or lactam). ^1H NMR ($CDCl_3$): δ 3.50 (3H, s, NMe), 4.06 (6H, s, 2 OMe), 6.33 (2H, s, OCH_2O), 7.19 (1H, d, J = 9.0 Hz, C-10), 7.33 (1H, s, C-3), 7.53 (1H, s, C-7), 8.36 (1H, d, J = 9.0 Hz, C-11). MS m/e (rel. int.): 337 (M^+, 100), 323 (M^+ − Me, 14.4), 322 (64.5), 294 (322 − CO, 8.7), 280 (294 − Me, 5.2), 279 (M^+ − CH_2O − CO, 26.2), 264 (279 − Me, 10.9). (Found: C, 67.41; H, 4.39; N, 3.90. Calc. for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15%)

The phenolic bases. Stesakine (**1**). Colourless columnar crystals (MeOH). UV λ_{max}^{EtOH} nm (log ε): 218 (4.47), 240 (sh, 4.10), 281 (4.23), 320 (sh, 3.69); $\lambda_{max}^{EtOH\ NaOH}$ nm (log ε): 235 (sh, 4.26), 313 (4.28), 327 (4.26). IR ($CHCl_3$) cm^{-1}: 3550 (OH). ^1H NMR ($CDCl_3$): δ 2.64 (3H, s, NMe), 3.83 (3H, s, OMe), 4.55 (1H, br., OH), 6.01 (2H, dd, J = 1.5, 9.0 Hz, OCH_2O), 6.55 (1H, s, C-3), 6.93 (1H, d, J = 9.0 Hz, C-10), 7.81 (1H, d, J = 9.0 Hz, C-11). MS m/e (rel. int.): 325 (M^+, 17.9), 324 (19.3), 323 (7.8), 308 (323 − Me, 5.1), 282 (M^+ − CH_2=NMe, 7.0), 149 (5.3). (Found: C, 67.25; H, 6.32; N, 3.80. Calc. for $C_{19}H_{19}NO_4 \cdot MeOH$: C, 67.21; H, 6.49; N, 3.92%)

O-Methylation of **1**. *O*-Methylation of **1** (17 mg) with ethereal CH_2N_2 by the usual method gave two *O*-methyl derivatives, colourless needles, mp 114-115°, $[\alpha]_D$ − 62.5° ($CHCl_3$, c 0.16), one of which was identified with an authentic sample of **2** by direct comparison (UV, IR, ^1H NMR, TLC, specific rotation and mmp).

Preparation of deuteriostesakine. **1** (28 mg) was heated with 5% NaOD · D_2O (2 ml) at 120° in a sealed tube for 20 hr. The reaction products were treated in the usual way, and gave an oily compound. Its ^1H NMR spectrum was compared with that of **1**: the doublet signal of the C-11 aromatic proton at δ 7.81 changed into a singlet and the signal of the C-10 aromatic proton at δ 6.93 disappeared.

Dehydrostesakine (**3**). Colourless columnar crystals (Me_2CO). UV λ_{max}^{MeOH} nm (log ε): 247 (sh, 4.32), 271 (4.73), 296 (sh, 4.12), 338 (4.10); $\lambda_{max}^{MeOH-NaOH}$ nm (log ε): 289 (4.69), 298 (4.66). IR ($CHCl_3$) cm^{-1}: 3500 (OH). ^1H NMR ($CDCl_3$): δ 3.10 (3H, s, NMe), 3.96 (3H, s, OMe), 5.88 (1H, s, OH), 6.14 (2H, s, OCH_2O), 6.66 (1H, s, C-3), 6.83 (1H, s, C-7), 6.99 (1H, d, J = 11.0 Hz, C-10), 8.62 (1H, d, J = 11.0 Hz, C-11). MS m/e (rel. int.): 323 (M^+, 54.8), 308 (M^+ − Me, 54.8), 280 (M^+ − CH_2=NMe, 100), 222 (86.8). (Found: C, 70.29; H, 5.23; N, 4.22. Calc. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33%)

O-Methylation of **3**. **3** (15 mg) in MeOH (7 ml) was treated with excess ethereal CH_2N_2 and kept at room temp. overnight. The desired product was purified by passing through a column of Si G (60) and recrystallization from EtOH gave colourless needles, mp 151–152°. This *O*-methyl derivative was shown to be identical with an authentic sample of **4** by comparison (UV, IR, ^1H NMR, TLC and mmp).

Bisaknadinine (**11**). Colourless columnar crystals (Me_2CO). ORD: $[\phi]_{295}$ − 81 203° (tr.), $[\phi]_{244}$ + 124 193° (pk). CD: $[\theta]_{315}$ + 45 378° (pk), $[\theta]_{265}$ − 102 698° (tr.), $[\theta]_{234}$ + 119 417° (pk). UV λ_{max}^{EtOH} nm (log ε): 263 (4.32), 293 (sh, 4.00). IR (KBr) cm^{-1}: 1660 (conj. CO), 3350 (OH). ^1H NMR ($CDCl_3$): δ 2.48 (2 × 3H, s, 2 NMe), 3.66, 3.83, 4.06 [2 (3 × 3H), s, 6 OMe], 6.06 (2 × 1H, br., 2 OH), 6.57 (2 × 1H, s, 2 Ar H). MS m/e (rel. int.): 716.8 (M^+, 24.1), 658 (M^+ − 58, 49.7), 600 (658 − 58, 20.9) [12]. (Found: C, 65.76; H, 6.79; N, 3.69. Calc. for $C_{40}H_{48}N_2O_{10} \cdot 2{\cdot}3H_2O$: C, 65.92; H, 6.82; N, 3.84%) These data and TLC identified the compound with authentic dimeric **11**, which was one of two stereoisomers (see below) afforded by treatment of **10** with $AgNO_3$ soln, and there was no mp depression on mmp.

Preparation of **11** *and its diastereoisomer from* **10**. To a soln of **10** (359 mg) in 30% aq. EtOH (12 ml), $AgNO_3$ (230 mg) in H_2O (12 ml) was added and the mixture was stirred at room temp. overnight. The product was made alkaline with aq. NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed, dried ($MgSO_4$) and evapd to leave an oily substance. This residue, purified by repeated column chromatography, afforded two compounds identified by IR spectrum. One of them on recrystallization from Me_2CO gave colourless columns, yield 150 mg. It had mp 196-198°, $[\alpha]_D$ − 288.8° ($CHCl_3$, c 0.19). Its spectra (UV, IR, ^1H NMR and MS) was identical with those of natural **11**. (Found: C, 65.83; H, 6.59; N, 3.63. Calc. for $C_{40}H_{48}N_2O_{10} \cdot 2{\cdot}3H_2O$: C, 65.92; H, 6.82; N, 3.84%) From the mother liquors a colourless oily substance was obtained showing a single spot on TLC. Its spectra (UV, IR, ^1H NMR and MS) were very closely similar to **11**, $[\alpha]_D$ − 125.0° ($CHCl_3$, c 0.24). ORD: $[\phi]_{295}$ − 62 208° (tr.), $[\phi]_{255}$ − 13 330° (pk), $[\phi]_{205}$ − 137 746° (tr.). CD: $[\theta]_{320}$ + 11 109° (pk), $[\theta]_{278}$ − 39 991° (tr.), $[\theta]_{218}$ + 44 434° (pk).

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