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NEW BISBENZYLISOQUINOLINES FROM *STEPHANIA PIERRII*

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ABSTRACT.—Among the alkaloids of the tubers of *Stephania pierrii* are the new bisbenzylisoquinolines (+)-2-norisotetrandrine [**1**], (+)-stepierrine [**2**], (+)-2′-norobaberine [**3**], (+)-stephibaberine [**5**], (+)-2′-norcepharanthine [**6**], (+)-2-norcepharanoline [**7**], and (−)-2-norisocepharanthine [**9**].

Stephania pierrii Diels (syn. *Stephania erecta* Craib) (Menispermaceae) is a slender, herbaceous climber with large tubers and round leaves. The tubers are used in Thai folk medicine as a skeletal muscle relaxant and also as an analgesic and tonic under the name "Bua Bok."

Previous work on the tubers showed the presence of the bisbenzylisoquinolines (+)-cepharanthine and (+)-homoaromoline (1).

We have carried out detailed studies on a sample of "Bua Bok" purchased from a traditional medicine drugstore in Bangkok. Three tetrahydrobenzylisoquinolines were found, namely, (+)-coclaurine, (+)-*N*-methylcoclaurine, and (+)-reticuline, as well as the aporphine (+)-isocorydine. A wide variety of bisbenzylisoquinolines was also obtained, among which were the head-to-tail dimers (−)-cycleanine and (−)-*N*-desmethylcycleanine, and the tail-to-tail dimers (+)-berbamunine and (+)-dehydroapateline.

Among the Menispermaceae, dimers of the isotetrandrine subgroup (8-7′, 11-12′) are quite common (2–4). In the present instance, several of these were obtained, namely, (+)-isotetrandrine (2–4), (+)-thalrugosamine (2–4), (+)-2-norberbamine (2–4), (+)-2′-norisotetrandrine (2–4), (+)-2-norisotetrandrine [**1**], and (+)-stepierrine [**2**]. The latter two alkaloids are new.

The mass spectrum of the nonphenolic (+)-2-norisotetrandrine [**1**], $C_{37}H_{40}N_2O_6$, was characteristic of a doubly bridged tail-to-tail dimer. The molecular ion, *m/z* 608, was of medium intensity, while the base peak, *m/z* 381, was due to the upper part of the dimer represented by rings A, B, A′, and B′. The 360 MHz nmr spectrum in $CDCl_3$ solution has been summarized around expression **1**. The spectral pattern was generally reminiscent of an isotetrandrine derivative with four methoxyl singlets (5). For isotetrandrine-type alkaloids, the N-2 methyl signal usually appears around δ 2.30 while the N-2′ methyl is at δ 2.55. (+)-2-Norisotetrandrine [**1**] showed only one *N*-methyl singlet at δ 2.57, so that a secondary amine must be present at N-2, i.e., on the left hand side of the dimer. The downfield shift of H-1 to δ 4.06 reinforced this assignment.

The uv spectrum of (+)-stepierrine [**2**], $C_{35}H_{32}N_2O_6$, showed bathochromic shifts in base as well as in acid (see Experimental) indicating the presence of a phenolic function and a fully aromatic isoquinoline moiety. This last feature was also manifested by a poor fragmentation in the mass spectrum where the base peak, *m/z* 575, corresponded to the $[M-1]^+$ ion. Additionally, the ^{1}H-nmr spectrum, as given around expression **2**, with an AB system at δ 7.32 and 8.33 ($J=5.6$ Hz), was typical of the pyridine ring of an isoquinoline system. The rest of the spectrum was very close to that for the known and related (−)-caryolivine, which has a methoxyl group

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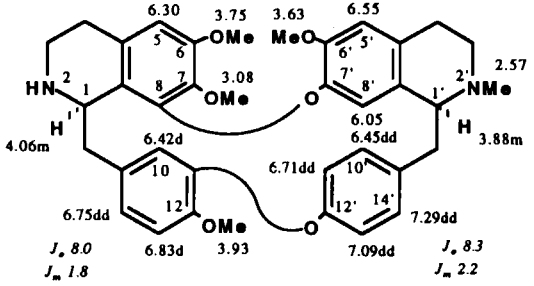

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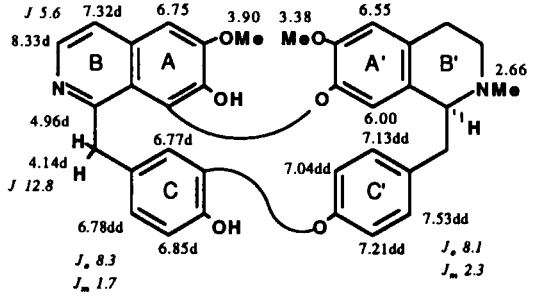

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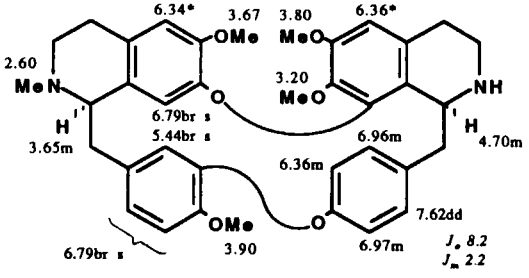

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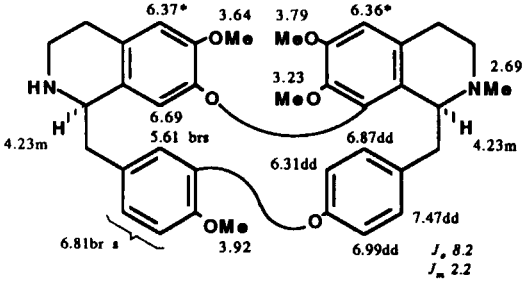
*Chemical shifts are interchangeable.



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*Chemical shifts are interchangeable.

at C-12 instead of a phenolic function (5).

(+)-2-Norisotetrandrine [**1**], with a moderate positive specific rotation, $[\alpha]_D$ +100° ($c = 0.16$, $CHCl_3$), possesses the same absolute configuration as (+)-isotetrandrine itself, 1*R*,1′*S* (6). (+)-Stepierrine [**2**], which is also dextrorotatory, $[\alpha]_D$ +55° ($c = 0.1$, $CHCl_3$), incorporates the 1′*S* absolute configuration that is the opposite configuration from the one possessed by (−)-caryolivine (7).

The remaining bisbenzylisoquinolines all belonged to the oxyacanthine subgroup (7-8′, 11-12′) and included (+)-obaberine (2), (+)-homoaromoline (2), (+)-aromoline (2), (+)-cepharanthine (2), (+)-2-norobaberine [**4**] (8), (+)-daphnandrine (2), (+)-2-norcepharanthine [**8**] (9), (+)-2′-norobaberine [**3**], (+)-stephibaberine [**5**], (+)-2′-norcepharanthine [**6**], (+)-2-norcepharanoline [**7**], and (−)-2-norisocepharanthine [**9**]. Of these twelve dimers, the last five, **3**, **5**–**7**, and **9**, are new.

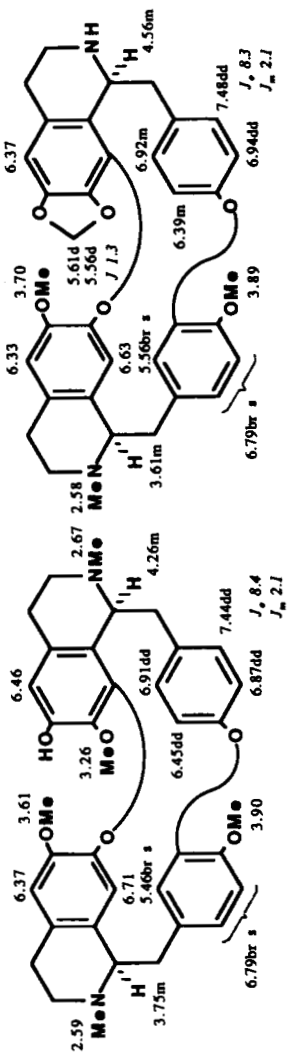
(+)-2′-Norobaberine [**3**], $C_{37}H_{40}N_2O_6$, presented nearly the same mass spectrum as (+)-2-norobaberine [**4**] with a molecular ion peak *m/z* 608 (42%) and a base peak *m/z* 381. The nmr spectrum (360 MHz, $CDCl_3$) displayed four methoxyl singlets at δ 3.20, 3.67, 3.80, and 3.90, and only one *N*-methyl singlet at δ 2.60, with an adjacent H-1 signal at δ 3.65. The H-1′ multiplet, by contrast, was situated downfield at δ 4.70, due to the presence of a secondary amine function in ring B′ (5).

The mass spectrum of the phenolic (+)-stephibaberine [**5**], $C_{37}H_{40}N_2O_6$, was close to that for dimer **3**. The molecular ion, *m/z* 608, and the base peak, *m/z* 381, were reminiscent of those for (+)-2′-norobaberine [**3**] or for (+)-2-norobaberine [**4**]. However, the nmr spectrum (360 MHz, $CDCl_3$) included two *N*-methyl singlets at δ 2.59 and 2.67 and only three methoxyl singlets at δ 3.26, 3.61, and 3.90, so that the phenolic function must be on the upper part of the molecule. The most upfield of the methoxyl singlets is due to the substituent at C-7′. The slight downfield shift of this signal compared to that for (+)-obaberine, as well as the absence of a methoxyl signal around δ 3.80, argued conclusively in favor of a phenolic function at C-6′ (5).

The methylenedioxy substituent occurs very seldom among bisbenzylisoquinolines (2–4). However, (+)-2′-norcepharanthine [**6**], (+)-2-norcepharanoline [**7**], and (−)-2-norisocepharanthine [**9**] all incorporated this functionality.

(+)-2′-Norcepharanthine [**6**], $C_{36}H_{36}N_2O_6$, displayed in the mass spectrum the same molecular ion as in the spectrum of (+)-2-norcepharanthine [**8**], *m/z* 592, as well as the same base peak, *m/z* 365 (9). The nmr spectrum showed the typical set of two close doublets, at δ 5.56 and 5.61 ($J = 1.3$ Hz) previously observed for the methylenedioxy group in the cepharanthine series (5). The sole *N*-methyl singlet was at δ 2.58, and the related H-1 multiplet was at δ 3.61. Looking at the opposite end of the molecule, the H-1′ signal appeared at δ 4.56, indicating that the secondary amine function involved N-2′ rather than N-2.

The phenolic (+)-2-norcepharanoline [**7**], $C_{35}H_{34}N_2O_6$, presented in its mass spectrum molecular ion *m/z* 578, which is 14 daltons less than for the known and accompanying (+)-2-norcepharanthine [**8**] (9). The mass fragment representing the top half of the molecule, *m/z* 365, was the same for species **7** and **8**, which allowed placement of the phenolic function at C-12. The nmr spectrum displayed one methoxyl singlet at δ 3.71 and the characteristic set of doublets at δ 5.60 and 5.64, indicative of a methylenedioxy at C-6′,7′. Only one *N*-methyl singlet was in evidence at δ 2.68. The adjacent H-1′ showed up as a multiplet at δ 4.20, while H-1 was represented by a multiplet at δ 4.27. The downfield shift of the latter from its usual chemical shift of ca. δ 3.60 was



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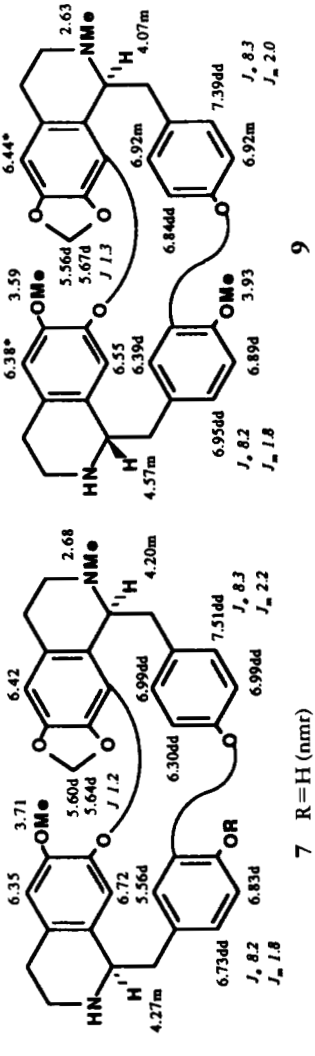

9

7 R=H (nmr)
8 R=Me

*Chemical shifts are interchangeable.

diagnostic of N-2 as a secondary amine (5).

Alkaloids **3**, **5**, **6**, and **7**, belonging to the oxyacanthine subgroup (7-8′, 11-12′), showed, as expected, strong positive specific rotations which confirmed their 1*R*, 1′*S* absolute configuration (6).

The mass spectrum of our last new alkaloid, (−)-2-norisocepharanthine [**9**], $C_{36}H_{36}N_2O_6$, was very close to that of (+)-2-norcepharanthine [**8**], with a molecular ion and base peak *m/z* 592, which was accompanied by strong ions *m/z* 365 and 183. However, the nmr spectrum of (−)-2-norisocepharanthine [**9**] was appreciably different from that of (+)-2-norcepharanthine [**8**] (5). In particular, H-10 appeared at δ 6.39 instead of δ 5.58. Also, H-1, which is adjacent to the secondary amine function, was at δ 4.57 instead of δ 4.32. The levorotatory character of (−)-2-norisocepharanthine [**9**], as well as the moderate magnitude of the specific rotation, $[\alpha]_D$ −84° (*c* = 0.25, $CHCl_3$), argued in favor of the 1*S*, 1′*S* configuration (6). Such an assignment also explains the differences between the nmr spectra of **9** on the one hand and **7** and **8** on the other (5).

(−)-2-Norisocepharanthine [**9**] is a minor alkaloid in the plant and is the only bisbenzylisoquinoline presenting this absolute configuration to be isolated from *S. pierrii*. It is possible, therefore, that its biogenesis involves oxidation of (+)-2-norcepharanthine [**8**] to the corresponding N-2 imine whose subsequent reduction then leads to C-1 epimerization. A finding of possible relevance in this context is that $NaBH_4$ reduction of (+)-coclobine or (+)-12-demethylcoclobine, which are oxyacanthine-type dimers with an imine at C-1, proceeds in a non-stereospecific manner to supply diastereomeric mixtures of the 2-nor derivatives (8,10).

EXPERIMENTAL

PLANT COLLECTION AND EXTRACTION, AND ALKALOID ISOLATION.—The dried tubers (10 kg) of *S. pierrii* were purchased from a traditional drugstore in Bangkok. A voucher specimen was deposited in the herbarium of the Department of Pharmacognosy, Chulalongkorn University. The powdered material was extracted first with petroleum ether and then with EtOH. After evaporation of the solvent, the EtOH extract was mixed with 10% HOAc in H_2O and filtered. Following basification with NH_4OH, the aqueous solution was extracted with $CHCl_3$. The organic layer furnished, after evaporation, 125 g of crude alkaloids. A rough separation was obtained by Si gel cc using a $CHCl_3$/MeOH gradient. Further purification of the alkaloids was achieved by cc using Si gel for tlc and through the use of Si gel tlc glass plates.

(+)-2-NORISOTETRANDRINE [**1**].—$C_{37}H_{40}N_2O_6$; eims $[M]^+$ 608 (48), 607 (41), 606 (10), 381 (100), 367 (13), 191 (71), 190 (10), 174 (17), 168 (15); hrms calcd for $[M]^+$ 608.2886, found 608.2893; uv λ max (MeOH) 208, 239 sh, 282 nm (log ε 4.82, 4.34, 3.86); $[\alpha]_D$ +100° (*c* = 0.16, $CHCl_3$).

(+)-STEPIERRINE [**2**].—$C_{35}H_{32}N_2O_6$; eims $[M]^+$ 576 (21), 575 (100), 288 (13), 192 (21), 191 (8), 190 (13), 177 (14), 174 (32); hrms calcd for $[M]^+$ 576.2260, found 576.2266; uv λ max (MeOH) 239 sh, 278, 331 nm (log ε 4.49, 3.97, 3.69); λ max (OH^-, MeOH) 264, 290 sh; λ max (H^+, MeOH) 230 sh, 263, 287 sh, 321, 371; $[\alpha]_D$ +55° (*c* = 0.10, $CHCl_3$).

(+)-2′-NOROBABERINE [**3**].—$C_{37}H_{40}N_2O_6$; eims $[M]^+$ 608 (42), 607 (42), 593 (9), 381 (100), 367 (20), 192 (7), 191 (54), 174 (19), 168 (17); hrms calcd for $[M]^+$ 608.2886, found 608.2894.

(+)-STEPHIBABERINE [**5**].—$C_{37}H_{40}N_2O_6$; eims $[M]^+$ 608 (45), 607 (27), 594 (1), 593 (4), 501 (6), 382 (26), 381 (100), 367 (25), 191 (54), 190 (13), 175 (11), 174 (36), 168 (31); hrms calcd for $[M]^+$ 608.2886, found 608.2880; uv λ max (MeOH) 241 sh, 283 nm (log ε 4.36, 4.00); λ max (OH^-, MeOH) 243 sh, 285 nm; $[\alpha]_D$ +207° (*c* = 0.17, $CHCl_3$).

(+)-2′-NORCEPHARANTHINE [**6**].—$C_{36}H_{36}N_2O_6$; eims $[M]^+$ 592 (22), 591 (23), 577 (4), 366 (24), 365 (100), 363 (14), 351 (14), 190 (10), 183 (49), 174 (19); uv λ max (MeOH) 210, 241 sh, 282 nm (log ε 4.61, 4.17, 3.71); $[\alpha]_D$ +206° (*c* = 0.24, $CHCl_3$).

(+)-2-NORCEPHARANOLINE [**7**].—$C_{35}H_{34}N_2O_6$; eims $[M]^+$ 578 (72), 577 (96), 576 (47), 575 (65), 366 (57), 365 (57), 351 (68), 349 (50), 206 (25), 192 (73), 183 (100); hrms calcd for $[M]^+$ 578.2417, found 578.2422; uv λ max (MeOH) 209, 242 sh, 283 nm (log ε 4.69, 4.16, 3.81); $[\alpha]_D$ +257° (*c* = 0.17, $CHCl_3$).

(−)-2-NORISOCEPHARANTHINE [**9**].—

$C_{36}H_{36}N_2O_6$; eims $[M]^+$ 592 (100), 591 (88), 365 (45), 351 (22), 349 (32), 206 (12), 192 (12), 183 (72), 160 (19); uv λ max (MeOH) 236 sh, 280 nm (log ε 4.08, 3.67); $[\alpha]_D$ −84° ($c = 0.25$, $CHCl_3$).

ACKNOWLEDGMENTS

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