

THE SYSTEMATIC CLASSIFICATION OF BISBENZYLISOQUINOLINES<sup>1</sup>

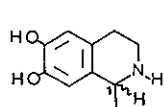
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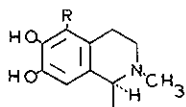
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Bisbenzylisoquinolines are classified into 26 types. Each benzylisoquinoline half is numbered as in expression 4 below, and is described in terms of its oxygenation pattern. The two sets of numbers denoting the oxygenated sites are separated by a hyphen. The more highly oxygenated benzylisoquinoline half constitutes the left hand side of the dimer, and is listed first. In the case of head to tail coupling, the more highly oxygenated benzylisoquinoline is placed on top, and is listed first. An asterisk (\*) or other symbol († or ‡) on the upper right of a number indicates the terminal of a diaryl ether. Numbers between parentheses, appearing directly after the listing of oxygenated sites, describe the positions of a biphenyl linkage. The stereochemistry of some of these alkaloids is also discussed.

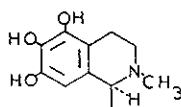
Although over 130 bisbenzylisoquinolines are presently known, new members of this assemblage of isoquinoline alkaloids continue to be isolated.<sup>2</sup> The building blocks for these natural products are usually (+)- and (-)-O-demethylcoclaurine (1), followed by the less common (+)-laudanosoline (2a) and (+)-thalinosoline (3). No cases are known where two laudanosoline units have dimerized, since the tendency for laudanosoline (or its di-O-methyl derivative reticuline) is to oxidize further to an aporphine or a protoberberine base.



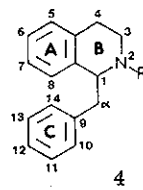
(+)-1, β H-1  
(-)-1, α H-1



2a, R = H  
2b, R = OH



3



4

Whenever a new bisbenzylisoquinoline is obtained, it is usually found to be a variation of a known alkaloid, differing simply in the nature of the oxygenated substituents (OH, OCH<sub>3</sub>, OCH<sub>2</sub>O), or the oxidation state or degree of substitution of the two nitrogen atoms (imine, pyridine, NH, NCH<sub>3</sub>, or 4<sup>0</sup> N), or yet in stereochemistry at the two asymmetric centers.

In some rarer cases, however, it is determined that the new bisbenzylisoquinoline differs from known analogs in a more fundamental way, such as in the number of aromatic oxygen substituents present, or else in the nature of the diaryl ether or biphenyl bond. On the basis of these more important differences, it is possible to classify systematically known bisbenzylisoquinolines into 26 types. These types can best be described by a numerical system obeying the following rules.

1. The numbering system for a benzylisoquinoline half of a dimer is as shown in expression 4. The lower aromatic ring, namely ring C, is always numbered so as to assign the smallest numbers to the substituents on that ring.
2. Each benzylisoquinoline half of the dimer is described in terms of its oxygenation pattern, since only oxygenated positions are indicated. The more highly oxygenated benzylisoquinoline half constitutes the left hand side of the dimer, and is listed first. The two sets of numerical values are separated by a hyphen. In the case of head to tail coupling, the more highly oxygenated benzylisoquinoline is placed on top, and is listed first.
3. The symbols \*, †, and ‡ indicate the shared oxygens of diaryl ethers, and are placed at the upper right of the appropriate numbers.
4. Numbers between parentheses, appearing after the listing of the oxygenated sites, denote a direct carbon-carbon bond for the presence of a biphenyl linkage. Numbers between squared brackets, appearing after the listing of the oxygenated sites, indicate the terminals of a methylenoxy bridge.

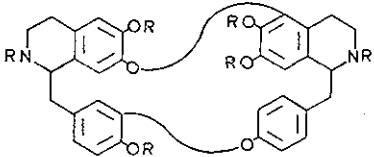
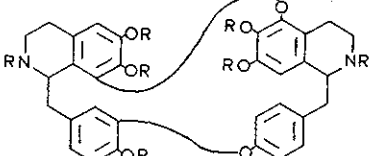
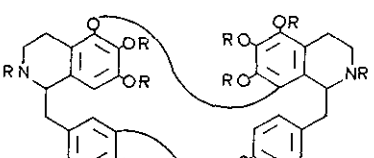
Using the above simple rules, the 26 types of bisbenzylisoquinolines can be denoted as indicated below.

Dimer	Type	Alkaloids
	6, 7, 11*, 12-6, 7, 12*	Dauricine, daurinolone, dauricinoline, dauricolone, magnoline, berbaminine, espinine, espinidine, lindoldhamine, thalibrine.
	6, 7, 11*, 12-6, 7*, 12	Liensinine, isoliensinine, neferine.
	6, 7, 8*, 11†, 12-6, 7†, 12*	Curine ≡ chondodendrine, tubocurine ≡ chondocurine, chondocurarine, chondrofoline, tubocurarine, hayatinine, hayatidine, cycleacurine.
	6, 7, 8*, 11†, 12-6, 7*, 12†	Berbamine, pycnamine, tetrandrine, isotetrandrine, phaeanthine, fangchinoline, limacine, obamegine, thalrugosine, penduline, atherospermoline, cycleadrine, cycleahomine, cycleanorine, krukovine, phaeantharine.
	6, 7, 8*, 11†, 12-6*, 7, 12†	Thalicberine, O-methylisothalicberine, thalmetine, helarine.

Dimer	Type	Alkaloids
	5*,6,7,11†,12-6*,7,12†	Nemuarine.
	5*,6,7,11†,12-6,7*,12†	Panurensine.
	5,6,7,8*,11†,12-6,7*,12†	Hernandezine, thalsimine, thalidezine.
	6,7,8*,11†,12,13-6,7*,12†	Tenuipine, isotenuipine.
	5,6,7,8*,10†,11,12-6,7*,12†	Thalibrunine, thalibrunimine.
	6,7,8*,11†,12,13-6,7*,12†[8-6]	Repanduline, pseudorepanduline.

Dimer	Type	Alkaloids
	6, 7, 10 <sup>*</sup> , 12, 13-6, 7, 12 <sup>*</sup>	Magnolamine
	6, 7, 8 <sup>*</sup> , 12-6, 7 <sup>*</sup> , 12(11-11)	Rodiasine, funiferine, ocotosine, tiliageine, phlebicine.
	6, 7 <sup>*</sup> , 8 <sup>†</sup> , 12-6 <sup>*</sup> , 7 <sup>†</sup> , 12(11-11)	Tiliacorine, tiliacorinine, nortiliacorine-A, nortiliacorinine-A and -B.
	6, 7, 8 <sup>*</sup> , 12 <sup>†</sup> -6, 7, 8 <sup>†</sup> , 12 <sup>*</sup>	Isochondodendrine, cycleanine, protocuridine, sciadenine.
	6, 7, 8 <sup>*</sup> , 12 <sup>†</sup> -6, 7, 8 <sup>†</sup> , 12 <sup>*</sup> [11-7]	Insularine, insulanoline.
	6, 7 <sup>*</sup> , 11 <sup>†</sup> , 12-6, 7, 8 <sup>*</sup> , 12 <sup>†</sup>	Oxyacanthine, ocoteamine, epistephanine, repandine, obaberine, demerarine, stebisimine, limacusine, aromoline, homoaromoline, thalmine, coclobine, thalrugosamine, daphnoline, cepharanoline, cycleapeltine, daphnandrine, sepeerine.

Dimer	Type	Alkaloids
	$6^*, 7^\dagger, 11^\ddagger, 12-6, 7^*, 8^\dagger, 12^\ddagger$	Trilobine, isotrilobine, micranthine, coculine, telobine, tricordatine, coccoline, trigilletimine.
	$6, 7^*, 8^\dagger, 11^\ddagger, 12-6, 7^\dagger, 8^*, 12^\ddagger$	Menisarine, cocsulinine.
	$6^*, 7, 11^\dagger, 12-6, 7, 8^*, 12^\dagger$	Thalicine
	$5, 6, 7, 8^*, 12^\dagger-6, 7^*, 11^\dagger, 12$	Thalispine, thalispidine, thalrugosaminine.
	$6, 7^*, 11^\dagger, 12-6, 7^\dagger, 11^*, 12$	Hayatine
	$6, 7, 8, 12^*-6, 7, 8^* [7-12]$	Cissampareine

<u>Dimer</u>	<u>Type</u>	<u>Alkaloids</u>
	6,7*,11†,12-5*,6,7,12†	Thalmine, dryadine, lauberine, dryadogaphnine, thalictine.
	6,7,8*,11†,12-5*,6,7,12†	Thalidasine, thalfoetidine, thalrugosidine.
	5*,6,7,11†,12-5,6,7,8*,12†	Thalfine, thalfinine.

The above classification system allows the precise description of the oxygenated skeleton of a bisbenzylisoquinoline without having resort to a structural diagram. In the case where both sides of a dimer bear an equal number of oxygens, the moiety appearing at the left or on top is that possessing the higher numbers, *viz.* for thalictine 6\*,7,11†,12-6,7,8\*,12† rather than the reverse notation 6,7,8\*,12†-6\*,7,11†,12. Whenever the numerical type description shows any position between 5 and 8 bonded to one between 9 and 14 in the other half of the dimer, this *ipso facto* can be taken as an indication that head to tail coupling is involved. It should be borne in mind that in nature no head to head coupling is encountered without accompanying tail to tail coupling.<sup>3</sup> In instances where a large ring has been formed through diaryl ether, or biphenyl or methylenoxy bridging, this ring is usually 18-membered, although rings as small as 16 or as large as 20 are also known.

The last type listed, 5\*,6,7,11†,12-5,6,7,8\*,12†, which includes thalfine and thalfinine,<sup>4</sup> is noteworthy because it is the only kind which incorporates two thalinosoline (3) units. However, added chemical and spectral evidence is required before the structures of these two alkaloids can be considered as settled. Another interesting type is 5,6,7,8\*,10†,11,12-6,7\*,12† which includes thalibrunine.<sup>5</sup> One half of this molecule incorporates the (+)-5-hydroxylaudanosoline unit (2b), the only such known case among all bisbenzylisoquinolines. It should be pointed out, however, that this same unit is fairly

common among aporphines (e.g. ocoteine) and aporphine-benzylisoquinolines (e.g. thalmineline). As in the case of (+)-laudanosoline (2a), no bisbenzylisoquinoline is likely to be found which incorporates two (+)-5-hydroxylaudanosoline units.

An important conclusion can be inferred from the above discussion. Whenever laudanosoline, 5-hydroxylaudanosoline, or thalinosoline dimerize to bisbenzylisoquinoline, or aporphine-benzylisoquinoline, or aporphine-pavine dimers, it is usually the (+)-rotating S-enantiomers represented by expressions 2a, 2b, and 3, respectively, that do so.<sup>6</sup> Thus, the absolute configuration of the thalinosoline units in such bisbenzylisoquinolines as thalfine and thalfinine,<sup>4</sup> as well as thalisopine, thalisopidine,<sup>7</sup> and thalrugosaminine,<sup>8</sup> can now be described for the first time, and must be as shown in expression 3.

#### References

1. This work was supported by NIH research grant CA-11450 awarded by the National Cancer Institute, PHS/DHEW.
2. For a listing of bisbenzylisoquinolines see T. Kametani, *The Chemistry of the Isoquinoline Alkaloids*, Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan (1974), p. 107.
3. If the numbering system for a benzylisoquinoline moiety needs to be differentiated from the other moiety, the left side or the upper side benzylisoquinoline is numbered 1, 2, 3, ..., while the right or lower side is numbered 1', 2', 3', ....
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6. An example of a rare exception to this rule is in the 6,7,8<sup>\*</sup>,11<sup>†</sup>,12,13-6,7<sup>\*</sup>,12<sup>†</sup> series, where (-)-laudanosoline forms part of such dimers as (-)-tenuipine and (+)-isotenuipine: I.R.C. Bick and W.I. Taylor, *J. Chem. Soc. (C)*, 1971, 3780.
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8. W.-N. Wu, J.L. Beal, G.W. Clark and L.A. Mitscher, *Lloydia*, 39, 65 (1976).

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