

THE STRUCTURE OF (+)-TILIARINE

HÉLÈNE GUINAUDEAU,¹ ALAN J. FREYER, MAURICE SHAMMA,

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

SUSIL K. MITRA, ANUP K. ROY, and BISWAPATI MUKHERJEE

Department of Pharmacology, B.C. Roy Post Graduate Institute of Basic Medical Sciences,
244B Acharya J.C. Bose Road, Calcutta 700020, India

The bisbenzylisoquinoline (+)-tiliarine, $C_{35}H_{34}N_2O_5$, is present in the roots of *Tiliacora racemosa* Colebr. (Menispermaceae) (1). It was known to be somehow structurally related to (+)-tiliacorine and its diastereomer (+)-tiliacorinine found in *T. racemosa* and related species (1).² Like tiliacorine and tiliacorinine, tiliarine incorporates a biphenyl bridge (C-11, C-11') in the bottom of the molecule, as well as two oxygenated bridges connecting rings A and A' (C-8, C-7' and C-7, C-6'). Additionally, two methoxyls and a phenolic function are present in each of the alkaloids. However, whereas tiliacorine and tiliacorinine possess two *N*-methyl groups, tiliarine contains one *N*-methyl and one NH group (1).

The mass spectrum of tiliarine (1) showed a strong molecular ion peak m/z 562 (74%) and an even stronger (M-1)⁺ ion peak m/z 561 (81%). The base peak, m/z 335, represents the top half of the molecule resulting from double benzylic cleavage. This fragmentation pattern is reminiscent of that observed for the related alkaloids (+)-2'-nortiliacorinine (2) and (+)-2'-nortiliacorine (3) (4).³

The nmr spectrum of (+)-tiliarine (1)

¹Permanent address: Faculté de Médecine et de Pharmacie, Université de Limoges, 87032 Limoges Cedex, France; or ERA 317, UER de Chimie Thérapeutique, Centre d'Etudes Pharmaceutiques, 99290 Chatenay-Malabry, France.

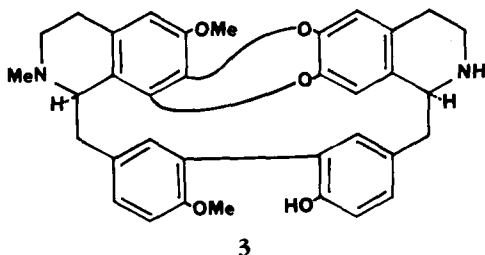
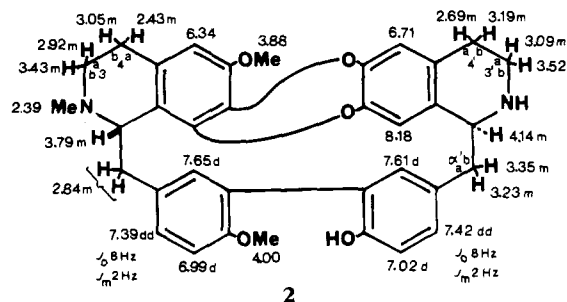
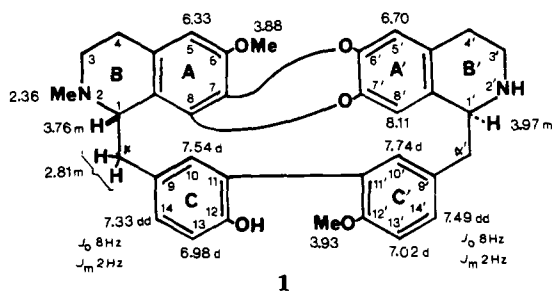
²For listings of the bisbenzylisoquinolines, together with their physical and spectral characteristics, see Guha *et al.* (2) and Schiff (3).

³Alternate names for (+)-2'-nortiliacorinine and (+)-2'-nortiliacorine are (+)-2-nortiliacorinine-A and (+)-2-nortiliacorine-A, respectively.

at 360 MHz in $CDCl_3$ is close to that of (+)-2'-nortiliacorinine (2). Both spectra show only one *N*-methyl singlet near δ 2.37 and two methoxyl singlets. A small but significant difference between them resides in the chemical shifts of the more downfield methoxyl signal (δ 3.93 for 1 and δ 4.00 for 2). Additional differences relate to the shifts for H-8', H-10, and H-10'. These aromatic protons are situated on the inside perimeter of the dimeric molecules and would be expected to be particularly sensitive to any change in the twist of the molecules due to an alteration in the nature of the aromatic substituents.

Presently, a complete nmr nOeds study (5) of 2'-nortiliacorinine allowed us to determine the chemical shifts for this dimer, including the critical values for the aliphatic protons attached to C-1, C-1', C- α , and C- α' . These assignments have been indicated around expression 2.

The close similarity in the nmr spectra of 2'-nortiliacorinine (2) and tiliarine (1), supplemented by a partial nOeds analysis of the nmr spectrum of tiliarine (1), led to the assignment of chemical shifts for all the critical protons in tiliarine. An important feature of this assignment is that it is possible to differentiate between the two ABX systems due to the aromatic protons of rings C and C'. Furthermore, it allowed for the placement of the bottom methoxyl substituent at C-12' rather than at C-12. In particular, irradiation of the 12'-methoxyl (δ 3.93) of tiliarine (1) led to a 10% enhancement of the H-13' doublet (δ 7.02) (see Experimental section).



Thus, the only difference between tiliarine (**1**) and 2'-nortiliacorinine (**2**) is in the relative positions of the hydroxyl and methoxyl substituents on rings C and C'.

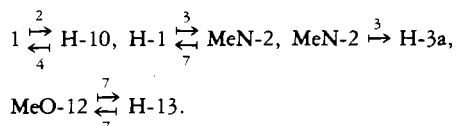
It is known that (+)-tiliacorinine and (+)-2'-nortiliacorinine possess the *S,S'* configuration (6). It may be considered a rule that, within a specific subgroup of the bisbenzylisoquinolines, the high resolution nmr spectra for species with the *S,S'* or *R,R'* configurations will show substantial differences in their overall patterns from their analogs of the *R,S'* or *S,R'* configurations (7). In the case of (+)-tiliacorinine (**1**), the nmr spectrum, as mentioned above, is very close to that of (+)-2'-nortiliacorinine (**2**), so that both dimers must incorporate the *S,S'* configuration.

EXPERIMENTAL

(+)-TILIARINE (**1**).—Uv λ max (MeOH) 235 sh, 289 nm (log ϵ 4.77, 4.15); ms m/z 562 (M^+ , 74), 561 (81), 349 (27), 336 (30), 335 (100), 321 (27), 168 (18); cd $\Delta\epsilon$ (nm) (MeOH) 0 (262), -8.2 (248), 0 (244), +10.4 (237), 0 (233), negative tail.

(+)-TILIARINE (**1**) NOEDS.—MeO-6 $\xrightarrow{11}$ H-5, H-10' $\xrightarrow{12}$ H-8', H-1' $\xrightarrow{1}$ H-8', H-10' $\xrightarrow{2}$ H-1', H- α $\xrightarrow{5}$ H-10, H- α $\xrightarrow{6}$ H-14, H- α $\xrightarrow{7}$ H-1, H-1 $\xrightarrow{8}$ MeN-2, MeO-12' $\xrightarrow{11}$ H-13'.

(+)-2'-NORTILIACORININE (**2**) NOEDS.—MeO-6 $\xrightarrow{9}$ H-5, H-4a $\xrightarrow{3}$ H-5, H-4'a $\xrightarrow{4}$ H-5', H-4'b $\xrightarrow{2}$ H-5', H-8' $\xrightarrow{8}$ H-10', H-8' $\xrightarrow{6}$ H-10, H- α 'a $\xrightarrow{2}$ H-8', H- α 'a $\xrightarrow{3}$ H-10', H- α 'a $\xrightarrow{3}$ H-1', H- α $\xrightarrow{4}$ H-10, H- α $\xrightarrow{7}$ H-14, H-



ACKNOWLEDGMENTS

This research was supported by grant CHE-8210699 from the National Science Foundation, and grant 355 from the International Foundation for Science (Sweden).

LITERATURE CITED

1. K.V.J. Rao and L.R. Row, *J. Org. Chem.*, **25**, 981 (1960).
2. K.P. Guha, B. Mukherjee, and R. Mukherjee, *J. Nat. Prod.*, **42**, 1 (1979).
3. P.L. Schiff, Jr., *J. Nat. Prod.*, **46**, 1 (1983).
4. A.N. Tackie and A. Thomas, *Planta Med.*, **16**, 158 (1968).
5. L.D. Hall and J.K.M. Sanders, *J. Am. Chem. Soc.*, **102**, 5703 (1980).
6. D.S. Bhakuni, A.N. Singh, S. Jain, and R.S. Kapil, *J. Chem. Soc., Chem. Commun.*, 226 (1978).
7. H. Guinaudeau, A.J. Freyer, and M. Shamma, *J. Org. Chem.* (*submitted*).

Received 15 March 1985