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STRUCTURE OF TILIAMOSINE: A NEW DIPHENYL BISBENZYLISOQUINOLINE ALKALOID FROM TILIACORA RACEMOSA

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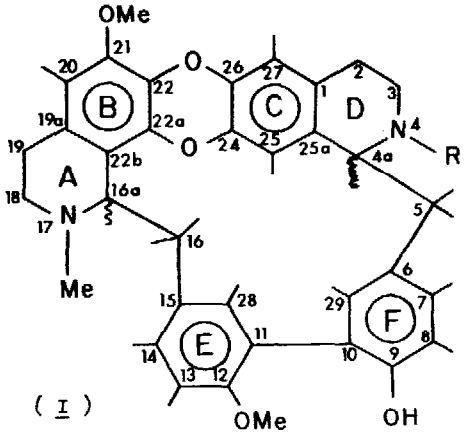
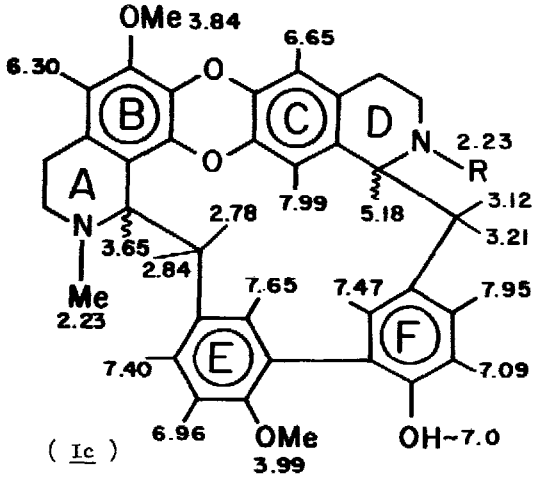
Several alkaloids [1] of unknown structures were isolated from the root bark of Tiliacora racemosa Colebr (Menispermaceae) a woody climber that grows in the subtropical regions of India where the plant is regarded as an antidote for snake bite [2]. From the same source two sets of diastereoisomeric alkaloids [3], tiliacorine and tiliacorinine $C_{36}H_{38}N_2O_5$ (Ia), as well as their respective N-demethylimino derivatives, nortiliacorinine A and B $C_{35}H_{34}N_2O_5$ (Ib), were also isolated. From degradation [3], mass spectral [4], nmr [3] and synthetic [5] studies these four alkaloids were assigned a common gross structure (I), namely dibenzo-p-dioxin containing bisbenzylisoquinoline moiety having a diphenyl unit. The diphenyl fragment [3] possesses a phenolic OH on one phenyl ring and a methoxy group on another ring. Although the relative positions of the two functions with respect to the two isoquinoline moieties were earlier deduced [3] to be the same in all four alkaloids, their exact locations remained unknown.

Recent pharmacological screening [6] on the methiodide of the crude alkaloid from the leaves [7] revealed a strong hypotensive effect which prompted us to undertake a detailed investigation of the crude extract. This resulted in the isolation of a new alkaloid, tiliamosine, $C_{36}H_{36}N_2O_6$ (II) as its N-acetate $C_{38}H_{38}N_2O_7$ (IIa), m.p. 276-277°(dec.), $[\alpha]_D^{27}$ + 530° ($CHCl_3$), m/e 634 (M^+) and nortiliacorinine A as a new derivative N-acetylnortiliacorinine A; $C_{37}H_{36}N_2O_8$ (Ic) m.p. 248-251° (dec.), $[\alpha]_D^{27}$ + 588° ($CHCl_3$) m/e 604 (M^+) as the major components. In fact this is the first report of the natural occurrence of N-acetylnortiliacorinine A. The mass fragmentation patterns of (IIa) contained besides the base peaks at m/e 634, intense ion peaks at m/e 408, 407, 366, 365, 351 and 183 which are typical of the biphenyl bisbenzylisoquinoline-p-dioxin alkaloids [4], indicating that tiliamosine (II) and (I) have a common gross skeletal structure. This conclusion is supported by the close similarities in their spectroscopic [3] and chemical data [3] as well as their common origin. Tiliamosine N-acetate (IIa), ν_{max}(KBr) 1640 cm^{-1} ($NCOCH_3$), gives positive color reactions for dibenzo-p-dioxin system [3] and Claisen's cryptophenol reagent test [8] for the phenolic OH group. Its IR absorption at 3360 cm^{-1}, bathochromic shift from $(EtOH)_{max}$ 292.5 nm (log e 4.08) to 305 nm (log e 4.01) in base, the formation of O-acetate, M^+ 676, ν_{max} 1762 ($OCOCH_3$) and 1642 cm^{-1} ($NCOCH_3$), confirms the presence of the phenolic OH group.

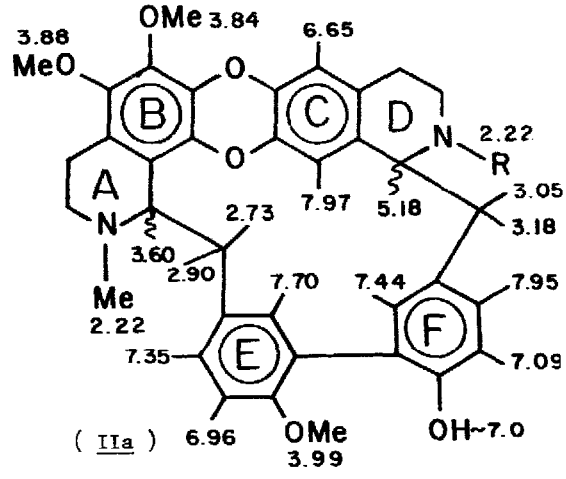


(I)

Ia	TILIACORINE or TILIACORININE	R = Me
Ib	NORTILIACORININE	A and B R = H
Ic	N-ACETYLNORTILIACORININE	A R = COMe
II	TILIAMOSINE	R = H
IIa	N-ACETYLTILIAMOSINE	R = COMe



(Ic)



(IIa)

In this communication we report the first part of our nmr study of tiliacora alkaloids It includes the structural identification of tiliamosine (II) and a general ^1H nmr scheme t determine the exact location of the substitution positions of the various substituents pres in tiliacora type alkaloids. Both these studies require precise structural assignments. H ever, this information is not *a priori* obvious even from high frequency ^{1})nmr normal spectr because the bisbenzylisoquinoline alkaloids posses a certain degree of symmetry. Therefore maialy through the examination of extensive spin decoupling and Nuclear Overhouse Effects (E.) experimental data the spectral information assigned. When selected proton resonance re goins are irradiated alternately with high and low r.f. power, the absorptions of the inter ing protons are significantly altered in several ways. The observed changes may be reflect in terms of resonance line-widths corresponding to spin-spin couplings and/or signal intens ties representing N.O.E.. Prior to conducting the various double resonance experiments, the MHz spectral data including the spin decoupling results were obtained in order to identify resonance positions of six protons representing the two set of methylene bridge protons and two methine neighbors situated on the two heterocyclic rings. Subsequent spectral analysis suggests that the two protons in both methylene bridge groups are distereotopic, and exhibi

12 Hz geminal as well as 11 and < 1 Hz vicinal spin interactions with their adjacent methin proton; thereby suggesting that their respective dihedral angle relationship is either ~ 1ℰ or ~ 0° and ~ 90°.

The comparison of 100 MHz spectra of (Ic) and (IIa) suggest, that the two compounds ar identical except for two significant differences: (Ic) contains nine aromatic protons whil (IIa) has only eight. There are two OMe groups in (Ic), while (IIa) possesses three. The singlet at δ = 6.30 and 6.65 in (Ic) and δ = 6.65 in (IIa) exhibit ~ 25% N.O.E. enhancement when benzylic methylene resonance regions in the respective spectra were irradiated; thereb indicating that these absorptions represent either H-20 or H-27. The unaffected singlets a δ = 7.99 and 7.97 in (Ic) and (IIa), respectively, are assigned to H-25 in the two samples. The resonance at δ = 6.30 in (Ic) was then assigned to H-20 on the basis of its ~ 20% N.O.E enhancement upon irradiation of OMe signal at δ = 3.84. Since H-20 resonance is absent in (IIa), the additional OMe in this sample must be located at C-20. Thus, tiliamosine (II), besides possessing the characteristic structural features of the tiliacorine type alkaloids also contains another distinctive feature, namely, the presence of an additional OMe group the benzocyclic ring B. (II) is the first dibenzo-p-dioxin containing bisbenzylisoquinolin alkaloid in which a benzocyclic ring possesses four ether oxygen atoms. Therefore, tiliamosine constitutes a new type of bisbenzylisoquinoline alkaloid.

Irradiation of the resonances of one set of methylene bridge protons whose chemical shifts are at lower fields than those of other methylene set, results in reduction of 0.2-0.3 Hz in the resonances line-widths of a doublet and a pair of doublets corresponding two aromatic protons as well as collapse of one of the two methine multiplets into a single Upon irradiation of this methine multiplet, H-25 singlet exhibits ~ 15% N.O.E. enhancement causes 0.1-0.2 Hz decrease in the line-width of H-27 singlet due a five-bond zig-zag coupli between the irradiated methine proton and H-27. The two preceding double resonance experiments clearly suggest that the irradiated methylene and methine absorptions must be due to two methylene protons at C-5 and H-4a, and the sharpened aromatic doublet and the pair of doublets represent H-29 and H-7, respectively. The identity of H-8 (ortho) doublet is reve ed upon irradiation of H-7 resonance. The three remaining undesignated aromatic resonances assigned to the three protons H-13, H-14, and H-28 located on ring E. The irradiation of OMe signal region in the spectrum of each tiliacora type alkaloid results in ~ 25% N.O.E. enhancement in H-13 doublet, thereby establishing the location of OMe on ring E. Thus by t process of elimination, the other substituent, namely, the phenolic OH, must be on ring F. This conclusion is in excellent agreement with an independent chemical study of tiliacora alkaloids by Professor Shamma[9] and his coworkers.

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