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Synthesis of Trisubstituted Dibenzazonine Alkaloids: Laurifine, Laurifinine and Laurifonine

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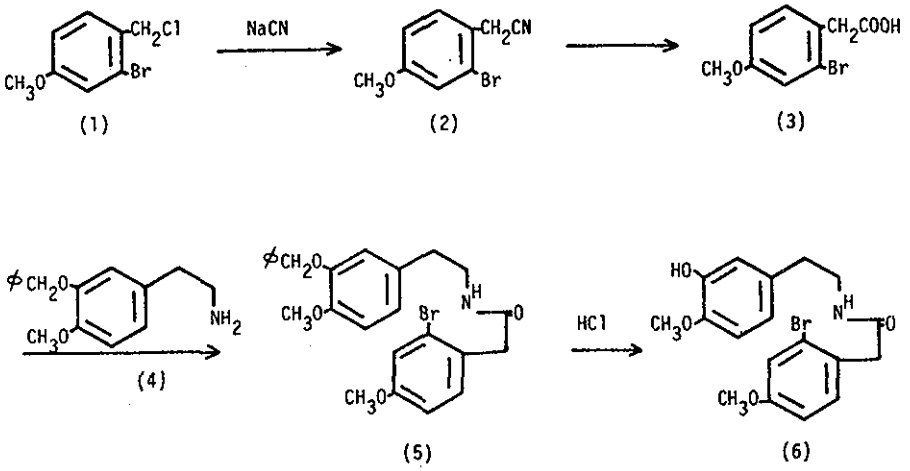
Irradiation of sodium salt of the phenolic bromo-compound (6) in methanol solution gave a mixture of three products (7, 8 and 9). Treatment of one of the photocyclization products (9) with methyl iodide-potassium carbonate followed by hydroboration with diborane afforded laurifine (11), which was readily converted into laurifonine (12) by N-methylation with formaldehyde-sodium borohydride. On the other hand, 9 was reduced with diborane to provide the secondary amine (13), and 13 was subsequently N-methylated to yield laurifinine (14). The synthetical laurifinine (14) was identical with natural laurifinine by comparison of various spectral data (ir, nmr and mass spectra) and t.l.c. behavior.

Bhakuni and his co-workers[1,2] have reported the isolation of three

dibenzazonine alkaloids from Cocculus laurifolius D.C. Two of them, named laurifine (11) and laurifinine, were shown to be respectively the de-N-methyl and de-O-methyl derivatives of the third constituent, laurifonine (12), whose structure was confirmed[1,2] by the spectroscopic evidence and the Hofmann degradation reaction. Furthermore, laurifonine (12) has been synthesized[3] by treatment of O-methylflavinantinol with boron trifluoride-etherate followed by hydrogenation. The structure (14) of laurifinine was proposed on biogenetic ground.[1] However, an alternative structure (15) for this alkaloid was postulated on the basis of spectroscopic evidence.[2] Therefore, the position of a hydroxyl group in the molecule of laurifinine would be ambiguous.[4]

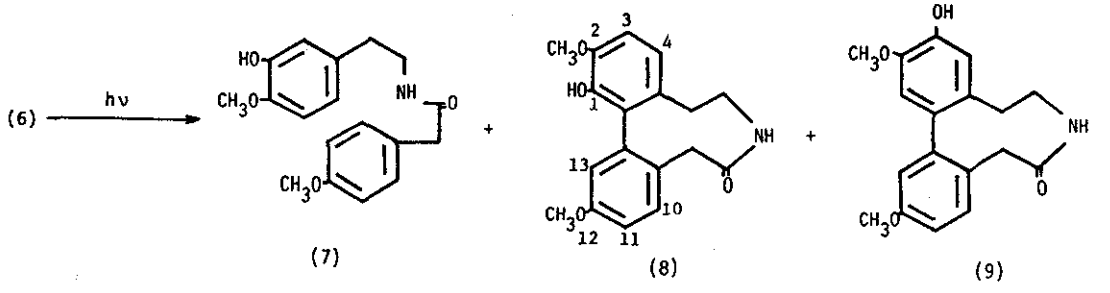
We wish to report on an efficient synthesis of these trisubstituted dibenzazonines (11, 12 and 14) and synthetic confirmation of the structure (14) of laurifinine.

The key reaction in the synthesis of three dibenzazonines was the photochemical cyclization of N-(3-hydroxy-4-methoxyphenethyl)-2-(2-bromo-4-methoxyphenyl)acetamide (6). The compound (6) was prepared as follows.



Treatment of 2-bromo-4-methoxybenzyl chloride (1)[6] with sodium cyanide in dimethyl sulfoxide at 90° for 2.5 hr afforded the cyanide(2)[7] [mp 56° IR $\nu_{max}^{CHCl_3}$ 2240 cm^{-1} (CN); 84 % yield], which was hydrolyzed under reflux with 5 % NaOH-H_2O to provide the corresponding carboxylic acid (3) [mp 127-128°, IR $\nu_{max}^{CHCl_3}$ 3480 (OH), 1730 cm^{-1} (C=O); 89 % yield]. The acid (3) was heated with 3-benzyloxy-4-methoxyphenethylamine (4)[8] in refluxing decalin to give an amide (5) [mp 134°, IR $\nu_{max}^{CHCl_3}$ 3380, 1660 cm^{-1} (NHCO); 91 % yield]. Debenzylation of 5 by reflux with aqueous 20 % HCl-EtOH afforded the expected bromo-phenolic compound (6) [mp 109°, IR $\nu_{max}^{CHCl_3}$ 3550 (OH), 3410, 1660 cm^{-1}(NHCO); 86 % yield].

Irradiation of 6 in methanol containing NaOH with 100 W high pressure mercury lamp at room temperature for 2 hr led to the formation of three products (7, 8 and 9), which were chromatographed on silica gel using a mixture of $CHCl_3$ and acetone (10 : 1) as an eluent. The structures of these substances were assigned on the basis of their spectral data.

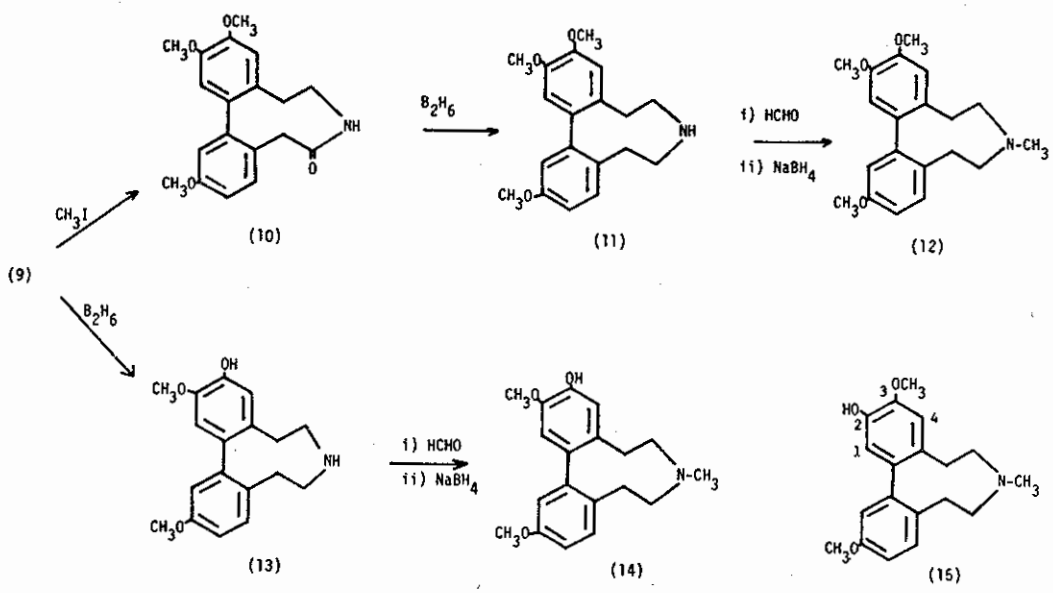


The primarily eluted substance (7) [$C_{18}H_{21}NO_4$, t.l.c.(Rf=0.55, silica gel/$CHCl_3$-acetone (3:1), mp 106°, IR $\nu_{max}^{CHCl_3}$ 3550 (OH), 3420, 1650 cm^{-1} (NHCO); nmr ($CDCl_3$) τ : 7.37 (2H, t, J=7 Hz, $ArCH_2CH_2N$), 6.57 (2H, t, J=7 Hz, $ArCH_2CH_2N$), 6.52 (2H, s, $ArCH_2CO$), 6.18, 6.13 (6H, 2 x OCH_3),

4.53 (1H, br.s, NH), 4.03 (1H, s, OH), 3.49 (1H, d.d, J=3, 9 Hz, ArH), 3.33 (1H, d, J=3 Hz, ArH), 3.27 (1H, d, J=9 Hz, ArH), 3.15 (2H, d, J=8 Hz, 2 x ArH), 3.88 (2H, d, J=8 Hz, 2 x ArH); MS m/e 315 (M^+): 16 % yield]

The secondary elution product (8) [$C_{18}H_{19}NO_4$, t.l.c. (Rf=0.34, silica gel/$CHCl_3$-acetone (3:1), mp 123°, IR $\nu_{max}^{CHCl_3}$ 3550 (OH), 3410, 1680 cm^{-1} (NHCO); nmr ($CDCl_3$) τ : 6.12, 6.08 (6H, 2 x s, 2 x OCH_3), 5.62 (1H, br.s, NH), 4.43 (1H, s, OH), 3.24 (1H, d, J=7 Hz, 3-H or 4-H), 3.22 (1H, d, J=3 Hz, 13-H), 3.09 (1H, d, J=7 Hz, 3-H or 4-H), 3.08 (1H, d.d, J=3, 8Hz, 11-H), 2.66 (1H, d, J=8 Hz, 10-H); MS m/e 313 (M^+); 14 % yield].

The third elution product (9) [$C_{18}H_{19}NO_4$, t.l.c. (Rf=0.25, silica gel/$CHCl_3$-acetone (3:1), mp 193-194°, IR $\nu_{max}^{CHCl_3}$ 3550 (OH), 3410, 1660 cm^{-1} (NHCO); nmr ($CDCl_3$) τ : 6.16 (6H, s, 2 x OCH_3), 4.14 (1H, s, OH), 4.02 (1H, br.s, NH), 3.24 (1H, s, 1-H or 4-H), 3.23 (1H, d, J=3 Hz, 13-H), 3.22 (1H, s, 1-H or 4-H), 3.08 (1H, d.d, J=10, 3 Hz, 11-H), 2.67 (1H, d, J=10 Hz, 10-H); MS m/e 313 (M^+); 27 % yield].



The photocyclization compound (9) obtained as the major product was treated with methyl iodide and potassium carbonate in anhydrous ethanol at 50° for 45 min to yield the O-methyl derivative (10) [mp 205-207°, IR $\nu_{max}^{CHCl_3}$ 3420, 1660 cm^{-1} (NHCO); MS m/e 327 (M^+); 90 % yield]. Hydroboration of 10 with sodium borohydride and boron trifluoride-etherate in dry tetrahydrofuran afforded laurifine (11) [oil; 98 % yield], whose spectral data was identical with those of the substance described in the literatures.[1,2] Furthermore, N-methylation of laurifine (11) with formaldehyde and sodium borohydride gave laurifonine (12) [oil, its perchlorate: mp 191°; 96 % yield], which was consistent with an authentic sample[1,2] obtained from the natural source.

Next 9 was converted into laurifinine (14). Reduction of 9 with sodium borohydride and boron trifluoride-etherate gave the corresponding secondary amine (13) [mp 185-187°, IR $\nu_{max}^{CHCl_3}$ 3540 cm^{-1} (OH); MS m/e 299 (M^+); 85 % yield], followed by N-methylation with formaldehyde and sodium borohydride to afford (14) [mp 179-181°, its perchlorate: mp 240-242° (lit,[1,2] mp 243-245°)]. The synthetic laurifinine (14) was proved to be completely identical with the authentic specimen of natural laurifinine, provided by Bhakuni, by their ir, nmr and mass spectral comparison, and t.l.c. behavior.

Further evidence for the structure of laurifinine was obtained by investigation of the nmr spectrum of its deuterium-labelling compound. The nmr spectrum of laurifinine exhibited two aromatic proton signals which were observed as two sharp singlets at 3.34 τ and 3.24 τ, respectively. The [$^2H_4$]-compound, prepared[9] by base-catalysed deuterium exchange of synthesized laurifinine (14) indicated disappearance of the signal of the aromatic proton at 3.24 τ. Hence the deuterium

exchange did not occur at C_1-position,[10] but at C_4-position. Consequently, the position of hydroxyl group in laurifinine must be located at C_3-position and the correct structure for laurifinine is represented by the formula (14).

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4 From the nmr spectral study[5] of erybidine and its analogues, methoxyl group which appeared at 6.08 τ in the tetrasubstituted dibenzazonine system was ascribed to C_3- and/or C_{11}-position. From this fact, the corresponding methoxyl group signal (singlet at 6.10 τ) in the trisubstituted dibenzazonine (laurifonine (12)) would be assigned to C_3-position. Since the nmr spectrum of laurifinine clearly showed the absence of the methoxyl group signal at 6.10 τ, the position of hydroxyl group in laurifinine would be preferably located at C_3-position.

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7 All new compounds were characterized by concordant analytical and spectral data.

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9 This [$^2H_4$]-compound [oil, MS m/e 314 (M^+), quantitative yield] was synthesized by heating in a sealed tube with 5 % NaOD-D_2O at 140° for 20 hr.

10 The aromatic proton, observed as a sharp singlet at 3.24 τ, was ascribed[2] to the C_1-position. According to Bhakuni's private communication, the assignment of this proton was erroneous for some confusion in interpretation of the nmr spectrum of laurifinine.

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