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ALKALOIDS OF MICHELIA FUSCATA BLUME: THE STRUCTURE AND SYNTHESIS OF MAGNOLAMINE

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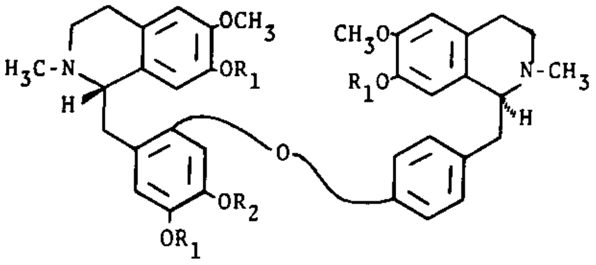
The cleavage reaction of triethylmagnolamine (3) by sodium-liquid ammonia determined the location of phenolic functions in magnolamine (2). Furthermore, the synthesis of magnolamine was carried out by the Ullmann reaction of two optically active compounds (10) and (12). The synthetic product was completely identical with natural magnolamine by comparison of various spectra and t.l.c. behavior. Thus, it was clarified that the structure of magnolamine is indicated by the formula (2).

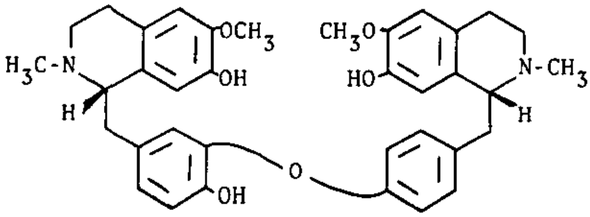
Magnolamine was isolated from the leaves of Magnolia fuscata Blume (synonym Magnolia fuscata Andr.) by Proskurnina et al[1] in 1938. The structure (1) of magnolamine was first proposed[2] on the basis of chemical methods. However, Tolkachev and his co-workers[3] later described that its structure ought to revise to (2) from the study on the nmr spectra of 4-ethoxy-5-methoxydiphenylether-2,4'-dicarboxylic acid, isolated as oxidation product of triethylmagnolamine (3), and its dimethyl ester.



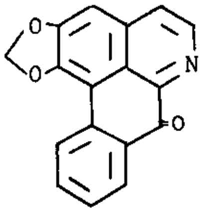
(1): $R_1 = R_2 = H$
(2): $R_1 = H$, $R_2 = CH_3$
(3): $R_1 = C_2H_5$, $R_2 = CH_3$
(4): $R_1 = R_2 = CH_3$
(5): $R_1 = CH_2Ph$, $R_2 = CH_3$

We wish to report herein the reconfirmation of the structure of magnolamine, which was afforded by the results of sodium-liquid ammonia cleavage reaction of triethylmagnolamine and the synthesis of magnolamine by utilization of the Ullmann reaction of compounds (10) and (12).

First, magnolamine was isolated[4] in the application[5] of multi-buffered paper chromatography method from the non-quaternary base portion of the leaves[6] of Michelia fuscata Blume, together with known two bases, a bisbenzylisoquinoline alkaloid, magnoline (6)[1,7] and an oxoaporphine alkaloid, liriodenine (7).[8]

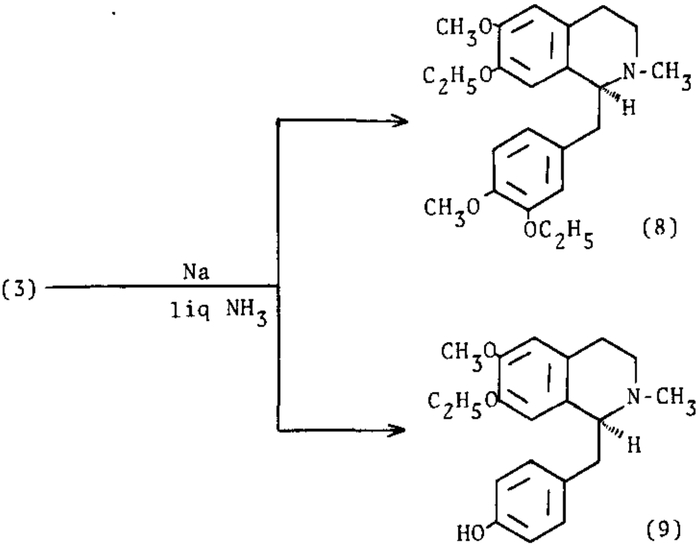


(6)



(7)

Magnolamine was converted to triethylmagnolamine[3] on treatment with diazoethane. The cleavage of triethylmagnolamine with metallic sodium in liquid ammonia at -72° , followed by purification of silica gel chromatography afforded the non-phenolic base (8) and the phenolic base (9).



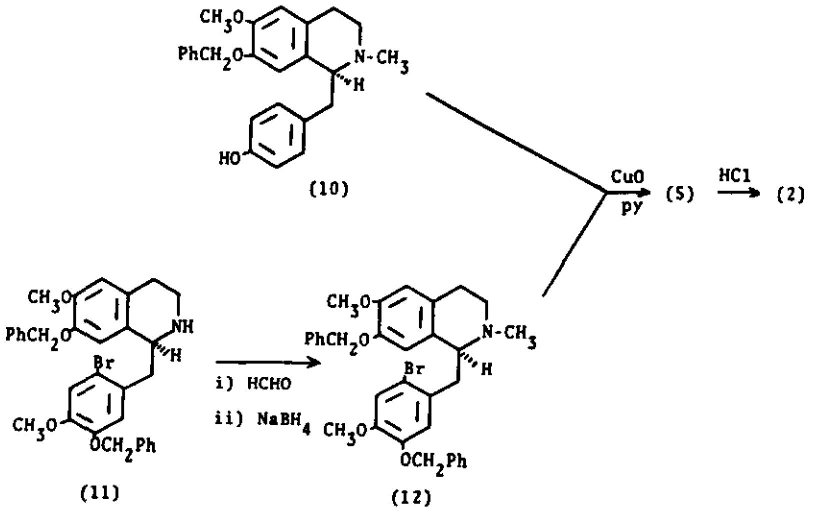
The non-phenolic product (8)(L-(+)-O,O-diethylreticuline)[$C_{23}H_{31}O_4N$, $[\alpha]_D$+33.9° (c=0.59, EtOH), nmr ($CDCl_3$) δ : 1.34, 1.42 (6H, 2 x t, J=7 Hz, 2 x $OCH_2\underline{CH_3}$), 2.50 (3H, s, N-CH_3), 3.78 (6H, s, 2 x OCH_3), 3.58-4.16 (4H, m, 2 x $O\underline{CH_2}CH_3$), 6.06 (1H, s, arom.H), 6.49-6.76 (4H, m, 4 x arom.H); MS m/z 385 (M^+), 220 (base peak); 23.7 % yield] was identical with the diethylated compound (78.6 % yield), which was obtained by ethylation of the synthesized <u>dl</u>-reticuline[9] with diazoethane, in comparison of their nmr ($CDCl_3$), ir ($CHCl_3$) and mass spectra.

On the other hand, the data of the phenolic product (9)(L-(+)-7-O-ethyl-N-methylcoclaurine)[$C_{20}H_{25}O_3N$, $[\alpha]_D$+64.8°(c=0.54,EtOH), ir ($CHCl_3$) cm^{-1}: 3630 (OH), nmr ($CDCl_3$) δ : 1.35 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.52 (3H, s, N-CH_3), 3.73 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 3.81 (3H, s, OCH_3), 6.06, 6.56 (2H, 2 x s, 2 x arom.H), 6.60, 6.89 (2H, 2 x d, J=8 Hz, 2 x arom.H); MS m/z 327 (M^+), 220 (base peak); 28.1 % yield] exhibited full identity with reported those.[10]

Thus, from the results of sodium cleavage of triethylmagnolamine, the location of phenolic hydroxyl groups in magnolamine was determined.

As the absolute configuration of two asymmetric carbons in magnolamine was already determined by sodium-liquid ammonia cleavage[2g] of trimethylmagnolamine (4) and the synthesis[2e] of its antipode <u>via</u> the Ullmann reaction, the results of our cleavage reaction of triethylmagnolamine supported the assertion[3] of Soviet group concerning the structure of magnolamine.

Finally, we carried out a total synthesis of magnolamine by the Ullmann reaction of two optically active 1,2,3,4-tetrahydroisoquinolines, L-(+)-7-O-benzyl-N-methylcoclaurine (10)[11] and L-(+)-6'-bromo-O,O-dibenzylreticuline (12). The bromo compound (12)[$C_{33}H_{34}NO_4Br$, mp 102°, $[\alpha]_D$+62.9° (c=1.24, $CHCl_3$); 73.7 % yield] was synthesized by N-methylation of the secondary amine (11), which was prepared according to the literature[12], with formalin and sodium borohydride. The mixture of (10) and (12) was refluxed in the presence of cupric oxide and potassium carbonate in dry pyridine for 24 hr under nitrogen atmosphere, and the resulting non-phenolic portion was chromatographed on silica gel (a mixture of $CHCl_3$ and MeOH (9 : 1) as an eluent) and alumina ($CHCl_3$) to give tribenzylmagnolamine (5)[$C_{58}H_{60}N_2O_7$, $[\alpha]_D$+40.6° (c=0.72, $CHCl_3$), nmr ($CDCl_3$) δ : 2.29, 2.43 (6H, 2 x s, 2 x N-CH_3), 3.61 (3H, s, OCH_3), 3.78 (6H, s, 2 x OCH_3), 4.76, 4.83, 4.92 (6H, 3 x s, 3 x $PhCH_2O$), 6.12, 6.19, 6.40, 6.54 (4H, 4 x s, 4 x arom. H), 6.48 (2H, s, 2 x arom.H), 6.64, 6.86 (4H, 2 x d, J=8 Hz, 4 x arom.H), 7.04-7.46 (15H, m, 15 x arom.H); mp 124°, characterized as picrate; 3.6 % yield].



Debenzylation of compound (5) with ethanolic concentrated hydrochloric acid yielded magnolamine [$[\alpha]_D$+110.9° (c=0.55, EtOH), ir ($CHCl_3$) cm^{-1}: 3550 (OH), nmr ($CDCl_3$) δ: 2.34, 2.43 (6H, 2 x s, 2 x $N\text{-}CH_3$), 3.72, 3.74, 3.77 (9H, 3 x s, 3 x OCH_3), 6.02, 6.19, 6.45, 6.48, 6.51, 6.65 (6H, 6 x s, 6 x arom.H), 6.68, 6.96 (4H, 2 x d, J=8 Hz, 2 x arom.H), MS m/z: 626 (M^+), 192 (base peak); 58.3 % yield]. The synthetic compound was completely identical with natural magnolamine by comparison of a variety of their spectra, optical rotation, and t.l.c. behavior. Therefore, it was proved that the structure for magnolamine is represented by the formula (2).

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