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A FACILE SEMISYNTHESIS OF LITEBAMINE, A NOVEL PHENANTHRENE ALKALOID, FROM BOLDINE VIA A BIOGENETICAL APPROACH

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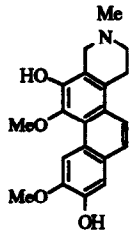
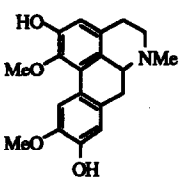
Summary: Litebamine was semisynthesized from boldine via a biogenetical approach. Main reactions include Von Braun reaction, exhaustive benzylation and Hofmann degradation in one pot, and the Mannich reaction.

In the recent communication,[1] we reported the structure elucidation of a novel phenanthrene alkaloid, litebamine (1), isolated from the barks of *Litsea cubeba* Persoon (Lauraceae). Comparing the structures of 1 and boldine (2), an aporphine existing in the same plant, we noted that 1 could be derived from 2 biogenetically via secoboldine (4) as intermediate. As part of a continuing investigation on this alkaloid, we report herein the preparation of 1 from this approach.

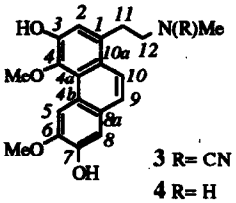
Compound 4 has been prepared from 2 directly by photolysis.[2] However, the reaction is not very practical because of the small scale limitation caused by the dilute reaction condition. To supply enough amount of 4 for the preparation of 1, two routes starting from 2, available from Sigma Co., were designed.



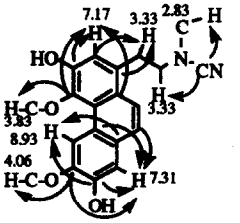
1



2



3 R= CN
4 R= H
5 R= Bn



COLOC results of 3

The Von Braun reaction of 2 by treatment with BrCN [3] in $CHCl_3$ under reflux gave *N*-cyanosecoboldine (3)[4] of 72% yield.[5] 3 shows ir absorption at 3392 cm^{-1} (OH) and 2214 cm^{-1} for NCN, uv maxima at 317.5, 305, 279 and 263 nm, characteristic of phenanthrenes.[6] Alkaline hydrolysis of 3 [KOH/ ethylene glycol- H_2O (4:1), Δ] produced 4 of 87% isolated yield. 4 shows identical physical data (mp, uv, ^1H nmr) [7] with secoboldine.[2] Although this route gave good yield of 4, the high polarity of 4 arises some separation problems. To scale up the production of 4, the second route was designed. We found that *N*-benzylsecoboldine (5), a less polar and easily handled intermediate, could be prepared from 2 in one pot reaction composed of exhaustive *N*-benzylation and Hofmann degradation. Thus, compound 5 [8] was isolated in 74% yield by refluxing 2 (1.00 g, 3.06 mmol) with BnCl (0.55 g, 4.35 mmol) in DMF (15 ml) for 2 h. The ^1H nmr spectrum of 5 shows *N*-benzyl group at δ 3.63 (s, CH_2) and 7.29 (m, C_6H_5). Its ms spectrum shows the base peak at *m/z* 134 [CH_2=N^+Me(Bn)],

obtained from β- cleavage of the parent molecular ion, characteristic fragmentation pattern of phenanthrene alkaloids.[9] Catalytical hydrogenation of **5** (H_2, Pd/C, HOAc, 50°, overnight) gave **4** in a good yield (>80%).

Compound **1** is prepared from **4** by the Mannich reaction. Under the usual manner (HCHO, HCl/ MeOH), no product was detected. After several attempts, we found the reaction run very smoothly under acetate buffer, pH 4.76, and MeOH at r.t. and produced **1**, mp. 218-220° from MeOH, in > 85% yield. The physical data (nmr, tlc, mp., ir, mass and uv) of **1** are identical to those of the natural product.[1]

The ^{13}C nmr spectrum of **4** has not been reported yet and was assigned by using **3** as the model compound. The COLOC, shown in the figure, and hetero-COSY spectra of **3** afford adequate information of C-H couplings and thus, allow the complete ^{13}C nmr assignment.[4] Following this, the ^{13}C nmr assignment of **4** was made.[6]

From this biogenetical approach, litebamine (**1**) is prepared from boldine (**2**) via three reaction steps in an overall yield of at least 50%. The pharmacological effects of **1** and the intermediates are currently investigated.

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2. J.B. Bremner and K.N. Winzenberg, *Aust. J. Chem.*, **1978**, *31*, 313 .
3. E.S. Smissman, A.C. Makriyannis, and E.J. Walaszek, *J. Med. Chem.*,**1970**, *13*, 640 .
4. The physical data of **3-5** were obtained from the following instruments: m.p. Fisher-Johns Melting Point Apparatus; ir: Perkin Elmer 1760-X Infrared FT spectrometer; uv: Hitachi 150-20 Double Beam Spectrophotometer; mass: Jeol JMS-HX110 Mass Spectrometer and Finnigan Mat 4500 series GC/MS at 70 eV; nmr: Bruker AC-80 and AM-300. Some physical data of **3**: mp. 53-54°; uv : λ_{max} (MeOH, log ε) 317.5 (3.96), 305.0 (3.93), 279.0 (4.35) and 263.0 (4.72) nm; ei-hrms m/z 352.1427 ($M^{+\cdot}$ for $C_{20}H_{20}O_4N_2$, calcd 352.1423), eims: *m/z* (rel. int. %) 352 ($M^{+\cdot}$, 69), 337 (15), 283 (100), 69 (53); ^1H nmr δ ($CDCl_3$) 7.17 (s, H-2), 8.93 (s, H-5), 7.31 (s, H-8), 7.48 (d, *J*= 9.1 Hz, H-9), 7.67 (d, *J*= 9.1 Hz, H-10), 3.33 (br s, H-11& H-12), 3.83 (s, 4-OMe), 4.06 (s, 6-OMe), 2.83 (s, NMe); ^{13}C nmr δ ($CDCl_3$) 131.2 (s, C-1), 116.9 (d, C-2), 147.1 (s, C-3), 142.2 (s, C-4), 124.2 (s, C-4a), 123.2 (s, C-4b), 107.6 (d, C-5), 146.8 (s, C-6), 145.7 (s, C-7), 111.0 (d, C-8), 128.7 (s, C-8a), 124.6 (d, C-9), 120.1 (d, C-10), 125.0 (s, C-10a), 31.4 (t, C-11), 53.6 (t, C-12), 60.1 (q, 4-OMe), 55.9 (q, 6-OMe), 39.2 (q, NMe), 118.0 (s, NCN).
5. We observed that if BrCN was added during reflux, the yield can be improved significantly from 42% up to 72% over the reported condition (at r.t.).
6. for review, see H. Guinaudeau, M. Leboeuf and A Cave, *J. Nat. Prod.* **1988**, *51*, 389 and references therein.
7. Some physical data of **4**: mp. 212° (dec) (lit.214° [2]); uv : λ_{max} (MeOH, log ε) 363 (2.74), 345(2.98), 317 (3.95), 304 (3.93), 280 (sh, 4.37) and 263 (4.74) nm; ei-hrms *m/z* 327.1460 ($M^{+\cdot}$ calcd for $C_{19}H_{21}O_4N$ 327.1471); ^1H nmr δ (DMSO-d_6) 7.12 (s, H-2), 9.00 (s, H-5), 7.20 (s, H-8), 7.43 (d, *J*= 9.1 Hz, H-9), 7.69 (d, *J*= 9.1 Hz, H-10), 3.19 (br s, H-11& H-12), 3.75 (s, 4-OMe), 3.90 (s, 6-OMe) and 2.57 (s, NMe); ^{13}C nmr δ (DMSO-d_6) 130.2 (s, C-1), 118.5 (d, C-2), 148.3 (s, C-3), 143.2 (s, C-4), 124.4 (s, C-4a), 123.2 (s, C-4b), 109.1 (d, C-5), 148.2 (s, C-6), 146.8 (s, C-7), 112.0 (d, C-8), 128.7 (s, C-8a), 124.4 (d, C-9), 120.7 (d, C-10), 124.9 (s, C-10a), 29.6 (t, C-11), 49.3 (t, C-12), 59.7 (q, 4-OMe), 55.9 (q, 6-OMe), and 32.9 (q, NMe).
8. Some physical data of **5**: amorphous solids; uv : λ_{max} (MeOH, log ε) 357.0 (2.98), 339.0 (3.15), 311.0 (3.99), 278.0 (4.39), 256.5 (4.72) nm; eims: *m/z* (rel. int. %) $M^{+\cdot}$ 417 (calcd for $C_{19}H_{21}O_4N$ 417, 6), 283 (10), 134 (100), 91 (56); ^1H nmr δ ($CDCl_3$) 7.12 (s, H-2), 8.92 (s, H-5), 7.28 (s, H-8), 7.42 (d, *J*= 9.1 Hz, H-9), 7.66 (d, *J*= 9.1 Hz, H-10), 3.24 (m, H-11), 2.77 (m, H-12), 3.82 (s, 4-OMe), 4.05 (s, 6-OMe) and 2.39 (s, NMe), 3.63 (s, N-$CH_2C_6H_5$), 7.29 (m, N-$CH_2C_6H_5$).
9. M. Shamma and J.L. Moniot, "Isoquinoline Alkaloids Research", **1978**, Plenum Press, New York, chp. 15.

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