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Recyclization of glaucine as a new route to litebamine derivatives

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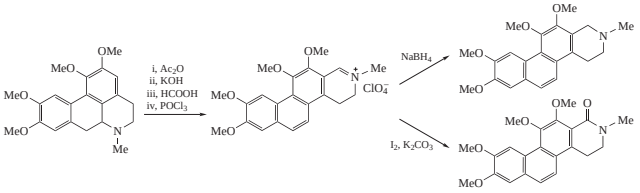
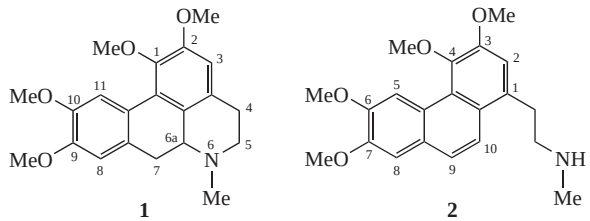
Using glaucine as an example, a convenient access to naphtho-[2,1-*f*]isoquinoline (litebamine) derivatives is proposed. The synthetic scheme involves a stepwise pyridine–pyridine recyclization of the intermediate *N*-acylsecoaporphine analogues.



Glaucine **1** as one of the most available aporphine alkaloids[1] is applied as an antitussive drug.[2] It is also used as a starting compound for the synthesis of other biologically active substances.[1(*a*),3] Its structure is challenging for the preparation of non-aporphine cyclic systems. Conversion of glaucine **1** to phenanthrene structures such as alkaloid secoglaucine **2** and its N-substituted derivatives by opening a tetrahydropyridine cycle in the course of C(6a)–N bond cleavage, proceeds easily. It can be caused by the action of electrophilic agents of acylating type[4] leading to *N*-acylsecoglaucines.

Phenanthrene backbone of the open forms of glaucine is potentially capable of back transforming to other tetracyclic systems by closing a hetero ring by reaction of aminoethyl group with one of the adjacent positions. The most obvious variant of such a cyclization is the formation of pyridine cycle at the 2-position.

If the new pyridine cycle forms in the step of cyclization, one can talk about pyridine–pyridine recyclization where the products should be derivatives of poorly studied heterocyclic system of naphtho[2,1-*f*]isoquinoline[5] close in structure to naphthoisoquinoline alkaloids, litebamine **3** and annoretine **4**.[6] According to the literature data, litebamine is capable of inhibiting acetylcholinesterase,[7] the formation of thromboxane B2[8] and adhesion of the cells of smooth musculature to collagen,[9] while annoretine has cytotoxity with respect to some types of cancer cells.[10]



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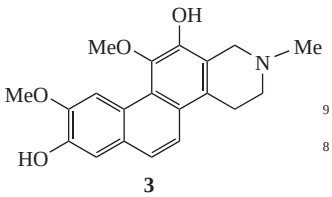

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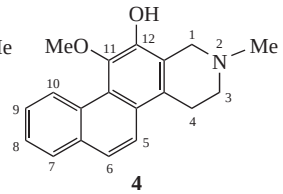

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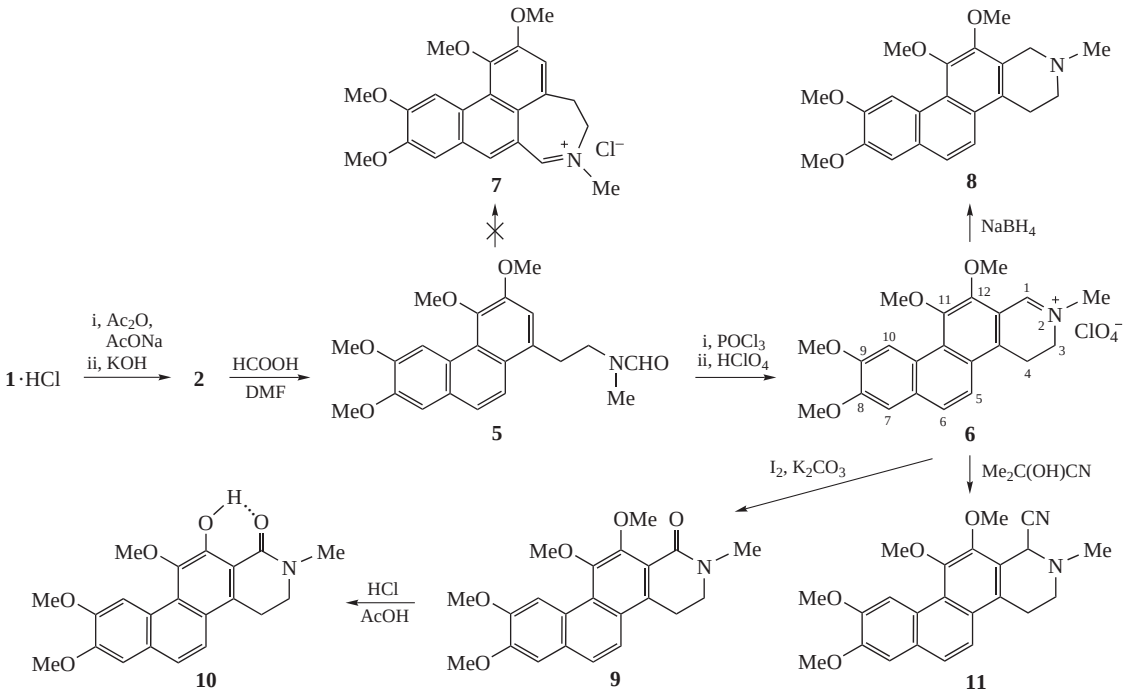
The pyridine–pyridine recyclizations of glaucine is not reported although for other aporphine alkaloids, namely, boldine and laurolitsine, similar transformations are known. They were carried out stepwise using formaldehyde as the cyclization agent and resulted in the formation of litebamine itself[11] or its homologues.[12] However, these reactions provide litebamines containing tetrahydropyridine moiety that is not prone to further facile transformations.

Recyclizations proceeding *via* the intermediate N-acylated secoalkaloids and their Bischler–Napieralski cyclization should be more promising. Indeed, such recyclizations should lead to naphthoisoquinoline structures of cyclic iminium type which have great potential for diverse transformations. Herein, we report on glaucine recyclization with participation of *N*-formyl secoglaucine **5**[13] (Scheme 1).

The initial step of recyclization, *viz.*, the opening of pyridine cycle in glaucine, was performed using acetic anhydride according to the improved procedure[4(*b*)] providing seco-derivative **2** in 90% yield. This seco-alkaloid upon the treatment with formic acid in DMF was converted into *N*-formyl derivative **5** (93% yield) that finally was cyclized with phosphorus oxychloride to 8,9,11,12- tetramethoxy-3,4-dihydronaphtho[2,1-*f*]isoquinolinium chloride formed in about quantitative yield. For convenience, this salt was treated *in situ* with $HClO_4$ to afford perchlorate **6** being an oxidized form of *O,O*-dimethyllitebamine and the first representative of quaternary salts of naphtho[2,1-*f*]isoquinolinium series (see Scheme 1).

The formation of salt **6** rather than isomeric azepinium perchlorate **7** was confirmed by the ^{1}H NMR spectrum (DMSO-d_6) of the product, which contained two doublets of 5- and 6-positioned protons at 7.89 and 7.94 ppm (*J* 9.3 Hz). The ultimate proof of the structure was provided by X-ray diffraction (XRD) study



Scheme 1

(Figure 1).† According to the XRD data, two from four methoxy groups, namely, in 11- and 12-positions, are characterized by strong distortion of conjugation of unshared electron pairs with the π-system of naphtho[2,1-*f*]isoquinoline. The reason of this phenomenon is steric hindrances created by hydrogen atoms at 1- and 10-positions towards MeO substituents.

The synthetic potential of salt **6** as the key structure for the preparation of O-derivatives of litebamine with unsubstituted 1-position and modified pyridine cycle was demonstrated using reduction, oxidation, and nucleophilic addition reactions (see Scheme 1).

The reaction of iminium perchlorate **6** with sodium borohydride in a water–alcohol medium leads to *O*,*O*-dimethyllitebamine **8**,

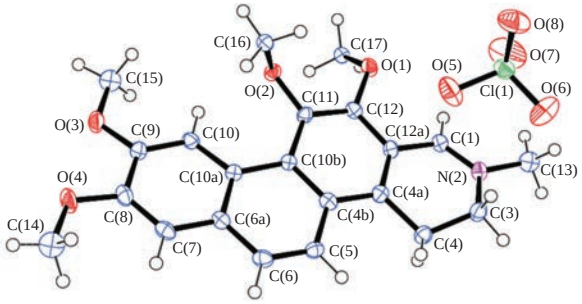


Figure 1 Molecular structure of salt **6** according to the XRD data.

the product of the C=N bond reduction in high yield (93%) (see Scheme 1). Its ^{1}H and ^{13}C NMR spectra agree with the structure **8**. This structure was also unambigously proved by the XRD method† (see Online Supplementary Materials). At the same time, the melting point (146–150 °C) of our substance strongly differs from that of the product obtained by reduction of 1-oxo-*O*,*O*-dimethyllitebamine **9** with lithium aluminium hydride (mp 64–68 °C),[17] although spectra of both compounds practically coincide. In this connection, one may suppose that another polymorph of tetrahydro derivative **8** was described in ref. 17.

The action of iodine on salt **6** in the presence of K_2CO_3 afforded oxo derivative **9** (73% yield). Its molecular structure was also confirmed by the XRD study.† Note that its melting point (187–190 °C) turned out to be higher than previously reported one[17] (146–149 °C), when oxo derivative **9** was obtained by multi-step scheme.

In compound **9**, the 12-positioned methoxy group seems suitable for demethylation due to the adjacent oxo fragment. In fact, oxo derivative **9** under rather mild protolytic conditions (reflux in AcOH/HCl) is selectively converted into mono-demethylation product, O(8)-methyllitebamine **10** in 75% yield (see Scheme 1). The ^{1}H NMR spectrum of the latter contains a low-field signal of OH group at 13.26 ppm indicating the chelation of its proton by intramolecular hydrogen bond. As follows from published data,[17] compound **9** behaves similarly towards BCl_3

† *Crystal data*. Single crystals were placed on a CCD area of Bruker SMART-APEX-II diffractometer under a steam of cooled nitrogen. Data reduction was performed using the Bruker SAINT program. The structures were solved by direct methods and refined by least squares in anisotropic approximation for non-hydrogen atoms. The hydrogen atoms were located from the difference Fourier synthesis and included in the refinement using riding model. Using Olex2,[14] the structure was solved with the ShelXT[15] structure solution program using intrinsic phasing and refined with the ShelXL[16] refinement package using least squares minimisation.

For **6**: $C_{22}H_{24}ClNO_8$ (M = 465.87), monoclinic, space group $C2/c$ (no. 15), a = 18.9337(17), b = 14.3989(13) and c = 15.6605(14) Å, β = 100.767(2)°, V = 4194.3(7) Å^3, Z = 8, T = 150 K, μ(MoKα) = 0.234 mm^{-1}, d_{calc} = = 1.476 g cm^{-3}, 15073 reflections measured (4.2° ⩽ 2θ ⩽ 49.376°), 3551 unique (R_{int} = 0.0398, R_σ = 0.0316) which were used in all calculations. The final R_1 was 0.0379 [$I > 2\sigma(I)$] and wR_2 was 0.0997 (all data).

For **8**: $C_{44}H_{50}N_2O_8$ (M = 734.86), triclinic, space group $P\bar{1}$ (no. 2), a = = 11.9595(5), b = 12.1265(5) and c = 13.4304(6) Å, α = 92.2450(10)°, β = 94.4250(10)°, γ = 105.2750(10)°, V = 1869.77(14) Å^3, Z = 2, T = 150 K, μ(MoKα) = 0.131 mm^{-1}, d_{calc} = 1.305 g cm^{-3}, 18121 reflections measured (4.488° ⩽ 2θ ⩽ 54°), 8157 unique (R_{int} = 0.0172, R_σ = 0.0221) which were used in all calculations. The final R_1 was 0.0443 [$I > 2\sigma(I)$] and wR_2 was 0.1325 (all data).

For **9**: $C_{22}H_{24}NO_4$ (M = 381.41), monoclinic, space group $P2_1/c$ (no. 14), a = 9.5177(6), b = 7.8704(5) and c = 24.4351(15) Å, β = 100.0110(10)°, V = 1802.5(2) Å^3, Z = 4, T = 150 K, μ(MoKα) = 0.100 mm^{-1}, d_{calc} = = 1.405 g cm^{-3}, 14358 reflections measured (4.346° ⩽ 2θ ⩽ 52.804°), 3663 unique (R_{int} = 0.0287, R_σ = 0.0257) which were used in all calculations. The final R_1 was 0.0383 [$I > 2\sigma(I)$] and wR_2 was 0.1087 (all data).

CCDC 1552311–1552313 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

giving an analogous boron chelate. Note that the closely located CO group can cause similar protodebenzylation.[18]

Salt **6**, owing to pronounced electrophilicity of its cation, readily adds hydrocyanic acid generated from acetone cyanohydrin. The reaction proceeds as addition of the nucleophile at the 1-position and affords the Reissert adduct of nonclassical type, 3-cyano-*O*,*O*-dimethyllitebamine **11**.

In conclusion, the stepwise pyridine–pyridine recyclization of N-substituted aporphine alkaloids passing through *N*-acylseco-aporphines according to the Bischler–Napieralski reaction, can be considered as the optimal choice for structural diversification of naphtho[2,1-*f*]isoquinoline derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.019.

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