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A novel synthesis of isoindolobenzazepine alkaloids: application to the synthesis of lennoxamine

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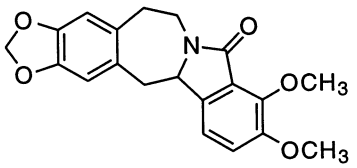
Abstract

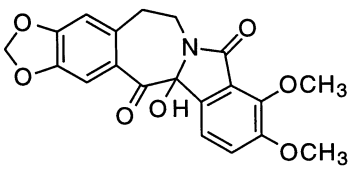
A novel, highly efficient synthesis of lennoxamine, a representative of isoindolobenzazepine alkaloid, is described.

Keywords: lennoxamine; isoindolobenzazepine.

Lennoxamine **1**[1] and chilenine **2**[2] are two representatives of a class of isoindolobenzazepine alkaloids.[3] Both compounds were first found in the plants of the Chilean *Berberis* species, lennoxamine was isolated from *Berberis darwinii* Hook while chilenine was found in *Berberis empetrifolia* Lam. Due to their unique structural features, the isoindolobenzazepine alkaloids[4] in general and chilenine[5,6] and lennoxamine[6,7] in particular, have captured the interest of many groups of synthetic chemists.



1



2

We have previously reported[4b] the synthesis of the isoindolobenzazepine (aporhoeadane) skeleton by using the route suggested by retrosynthetic analysis as shown in route A. However, attempts to apply this route to the synthesis of more complex oxygenated natural products

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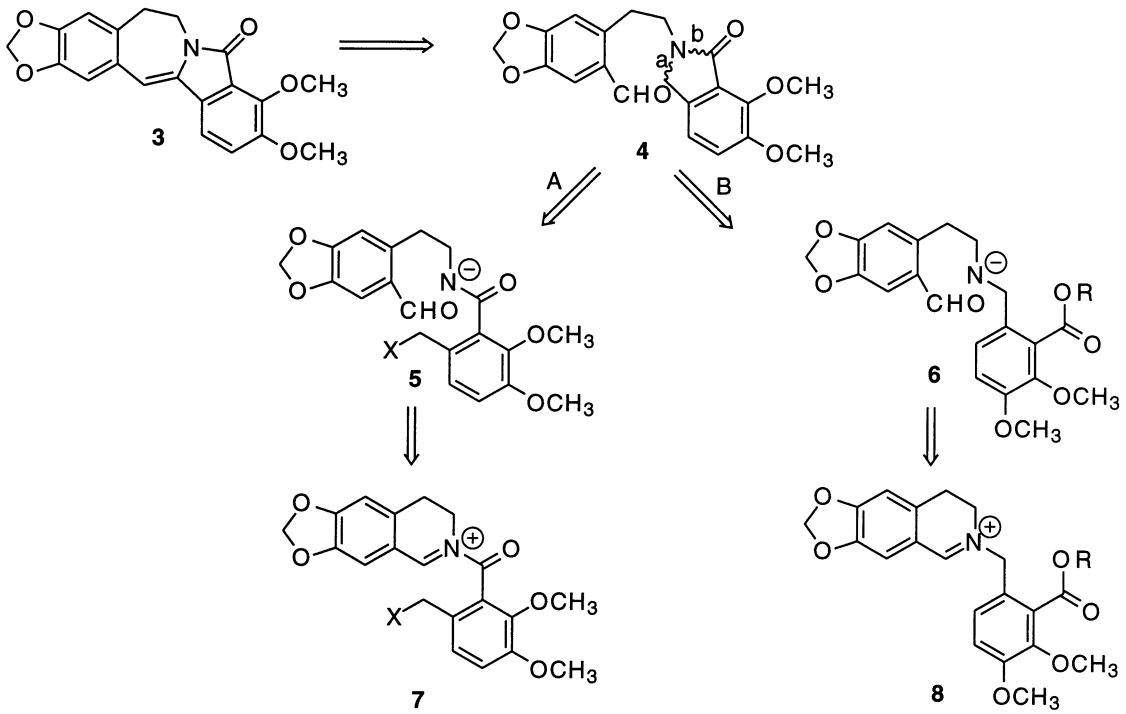
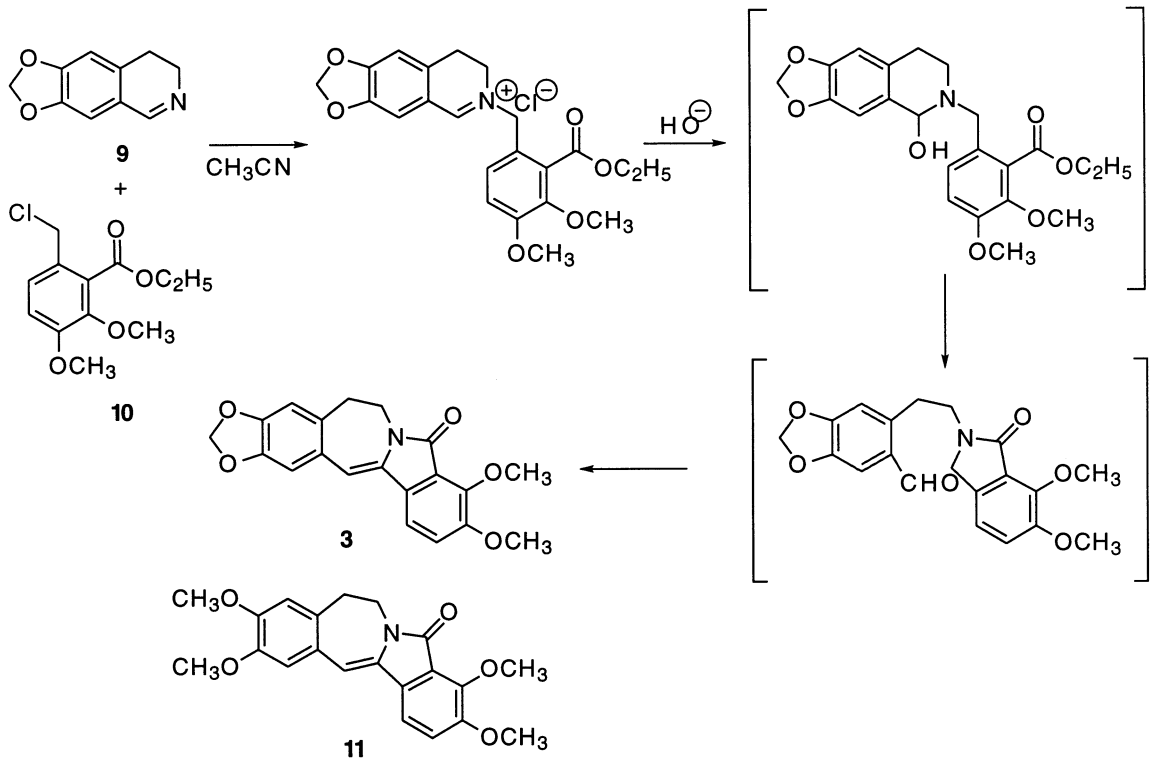
required the synthesis of not readily accessible halomethylbenzoyl chlorides. We have also found that when 6,7-methylenedioxy-3,4-dihydroisoquinoline was used as one of the components in the reaction with chloromethylbenzoyl chloride, the required lactam was obtained in disappointing yield. We have now solved the above drawbacks and successfully applied a new approach to the synthesis of lennoxamine.

Our retrosynthetic analysis is shown in Scheme 1. Breaking of the carbon–carbon double bond of the benzazepine skeleton in dehydrobenzazepine **3** leads to the lactam intermediate **4**. In our previous analysis, this lactam intermediate would be formed by the intramolecular alkylation of the amide intermediate **5** in route A. However, the alternative breaking of bond b in route B leads to the amino aldehyde intermediate **6**, i.e. the formation of the lactam would involve the reaction of an amine and an ester. It was expected that formation of the amide bond via route B would be more facile than the alkylation in route A due to the basicity of the nitrogen which is an amine in route B and an amide moiety in route A. Intermediates **5** and **6** could be obtained from acyliminium salt **7** or benzyliminium salt **8**, respectively.



Scheme 1.

In order to test the validity of the above mentioned idea, lennoxamine was synthesized as shown in Scheme 2. Alkylation of the 6,7-methylenedioxy-3,4-dihydroisoquinoline **9** with the readily available ethyl 6-chloromethyl-2,3-dimethoxybenzoate[8] **10** in acetonitrile gave the required iminium chloride. The iminium chloride so obtained was not isolated but was treated with potassium hydroxide or sodium hydroxide. It was indeed gratifying to find that the iminium salt was smoothly converted directly to dehydrolennoxamine **3** in 73% yield by potassium hydroxide and in 58% yield by sodium hydroxide. The presumed pseudobase and the aldehydic lactam intermediates were not isolated in the reaction.



Scheme 2.

By replacement of 6,7-methylenedioxy-3,4-dihydroisoquinoline with 6,7-dimethoxy-3,4-dihydroisoquinoline in the above reaction, the analogue of the dehydrolennoxamine **11** was successfully synthesized in 75% overall yield. Dehydrolennoxamine and its analogue were hydrogenated with 10% palladium on carbon in ethyl acetate to give lennoxamine and its analogue[9] in 76 and 80% yields, respectively.

Acknowledgements

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9. All compounds have been fully characterized. Dehydrolennoxamine **3**: m.p. 208–209°C; IR (nujol) 1690, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.0 (t, 2H, $J=4.9$ Hz), 3.95 (s, 3H), 4.08 (s, 3H), 6.00 (s, 2H), 6.35 (s, 1H), 6.68 (s, 1H), 6.80 (s, 1H), 7.12 (d, 1H, $J=8$ Hz), 7.48 (d, 1H, $J=8$ Hz). ^{13}C NMR (100 MHz) δ 35.39, 41.72, 56.62, 62.38, 101.19, 104.87, 110.06, 110.18, 114.28, 116.24, 120.22, 127.71, 130.99, 133.16, 133.83, 146.49, 146.72, 146.82, 152.82, 163.58. EIMS 351(100), 336(20), 322(10), 175(7). Anal. calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.84; N, 3.98. Found: C, 68.50; H, 4.80; N, 3.95. Dehydrolennoxamine analogue **11**: m.p. 185–189°C; IR (nujol) 1690, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (t, 2H, $J=4.6$ Hz), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.08 (s, 3H), 6.35 (s, 1H), 6.65 (s, 1H), 6.81 (s, 1H), 7.09 (d, 1H, $J=8.4$Hz), 7.39 (d, 1H, $J=8.4$ Hz). ^{13}C NMR (100 MHz) δ 35.18, 41.62, 55.87, 56.62, 62.35, 104.97, 113.02, 113.70, 114.21, 116.27, 120.25, 126.44, 131.05, 132.50, 133.17, 146.70, 147.44, 148.00, 152.74, 163.64. EIMS 368(31), 367(100), 353(16), 352(65), 308(9), 184(8). Anal. calcd for $C_{21}H_{21}NO_5$: C, 68.66; H, 5.72; N, 3.81. Found: C, 68.60; H, 5.72; N, 3.83. Lennoxamine **1**: m.p. 226–227°C; Lit[1], 225°C; Lit[7]a, 228–229°C; IR (nujol) 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (m, 2H), 2.93 (m, 2H), 3.10 (dd, 1H, $J=14.7$, 1.7 Hz), 3.92 (s, 3H), 4.10 (s, 3H), 4.30 (dd, 1H, $J=10.5$, 1.3 Hz), 4.74 (m, 1H), 5.95 (d, 1H, $J=1.47$), 5.96 (d, 1H, $J=1.47$), 6.71 (s, 1H), 6.78 (s, 1H), 7.13 (d, 1H, $J=8.2$ Hz), 7.18 (dd, 1H, $J=8.8$, 0.4 Hz). ^{13}C NMR (100 MHz) δ 35.93, 41.11 42.71, 56.75, 60.17, 62.54, 101.04, 110.34, 110.34, 116.26, 117.05, 124.18, 130.94, 134.85, 138.22, 146.08, 146.35, 147.26, 152.63, 165.18. EIMS 354(29), 353(96), 352(20), 338(51), 335(27), 162(69), 161(100), 160(29), 149(27), 131(47). Anal. calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.38; N, 3.96. Found: C, 67.83; H, 5.42; N, 3.97. Lennoxamine analogue: m.p. 213–214°C; IR (nujol) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (m, 2H), 2.95 (m, 2H), 3.13 (dd, 1H, $J=14.5$, 1.6 Hz), 3.90 (s, 3H), 3.92 (s, 3H), 3.915 (s, 3H), 4.11 (s, 3H), 4.32 (dd, 1H, $J=10.7$, 0.5 Hz), 4.76 (m, 1H), 6.74 (s, 1H), 6.82 (s, 1H), 7.14 (d, 1H, $J=8.2$ Hz), 7.21 (dd, 1H, $J=8.2$, 0.5 Hz). ^{13}C NMR (100 MHz) δ 35.80 41.19, 42.64, 55.95, 56.06, 56.66, 62.44, 113.46, 113.68, 116.15, 117.02, 124.10, 129.72, 133.67, 138.28, 146.70, 147.14, 147.14, 147.46, 152.53, 165.11. EIMS 370(20), 369(85), 353(44), 351(29), 177(100). Anal. calcd for $C_{21}H_{23}NO_5$: C, 68.29; H, 6.23; N, 3.79. Found: C, 68.38; H, 6.32; N, 3.77.