Study on the Ring Eulargment Reaction: Synthesis of 7,8,13, 13a-tetrahydroisoindolo[1,2-b][3]benzazepine and 5,6,8,9,14,14a-hexahydroisoquino[1,2-b][3]benzazepine

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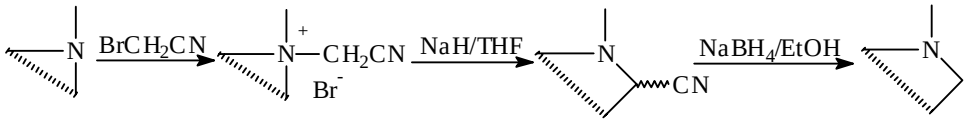
Abstract: A new approach to the synthesis of 7,8,13,13a-tetrahydroisoindolo[1,2-b][3]benzazepine **5** and 5,6,8,9,14,14a-hexahydroisoquino[1,2-b][3]benzazepine **9** and related compounds is described as using ring expansion of N-heterocycles.

Keywords: Ring enlargement, isoindolo[1,2-b][3]benzazepines, isoquino[1,2-b][3]benzazepines, synthesis.

In our research on the ring enlargement of certain N-heterocycles, a general procedure for the ring enlargement with the insertion of an extra -CH_2- was improved and shown in **Scheme I**[1].

Scheme I



The procedure had been carried out with such N-heterocycles as 2-methyl-1,2,3,4-tetrahydroisoquinoline[2], tetrahydroberberine and strychnine[3] with expected results. Thus, the procedure shown in **Scheme I** provides a new approach to the synthesis of larger N-heterocycles.

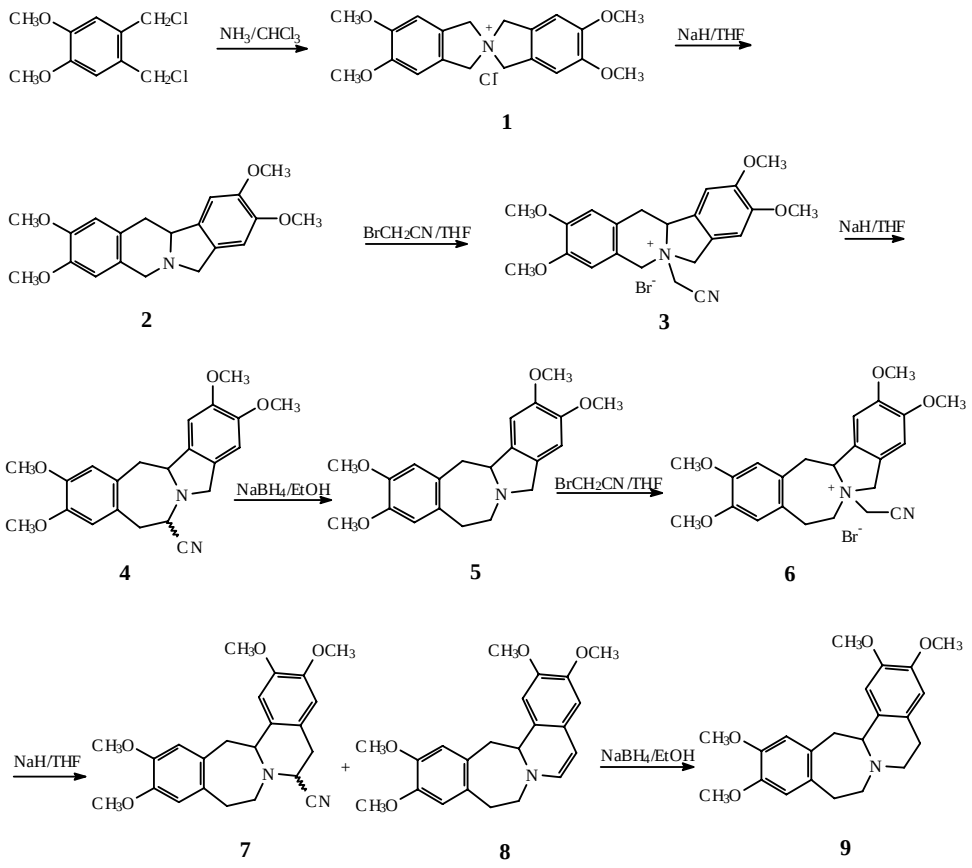
Isoindolo[1,2-b][3]benzazepines and isoquino[1,2-b][3]benzazepines are two basic structure skeletons in the natural alkaloids such as lennoxamine, puntarenine and salutine. Although biogenetically related to protoberberine, the presence of benzazepine systems is characteristic.

Previous literatures had reported several approaches to the synthesis of benzazepine systems, but generally based on the cyclization of linear or macrocyclic precursors[4,5]. Herein we report a new approach to the synthesis of substituted

7,8,13,13a-tetrahydroisoindolo-[1,2-b][3]benzazepine **5** and 5,6,8,9,14,14a-hexahydroisoquino[1,2-b][3]benzazepine **9** based on ring expansion.

As shown in **Scheme II**, the key intermediate, (±)-2,3,9,10-tetramethoxy-5,7,11b,12-tetrahydroisoindolo[2,1-b]isoquinoline (**2**), was prepared *via* 2 steps from bis(chlorometh-yl)veratrole by literature procedures[6]. As a result, the ring enlargement of **2** by the procedures of alkylation, Stevens rearrangement and reductive decyanation gave (±)-2,3,10,11-tetramethoxy-7,8,13,13a-tetrahydroisoindolo[1,2-b][3]benzazepine(**5**). Similarly, ring enlargement of **5** gave (±)-2,3,11,12-tetramethoxy-5,6,8,9,14,14a-hexahydroisoquino- [1,2-b][3]benzazepine (**9**).

Scheme II



Results and Discussions

Following literature procedures[6], bis(chloromethyl)veratrole react with NH_3 in $CHCl_3$ to give the spiro quaternary ammonium salt **1** in 40% yield. As a symmetric molecule, **1**

underwent Stevens rearrangement to give (±)-2,3,9,10-tetramethoxy-5,7,11b,12-tetrahydro-isoindolo[2,1-b]isoquinolinium (**2**)[7] as the only product with 80% isolated yield.

2 reacted with $BrCH_2CN$ in anhydrous THF to give the cyanomethyl quaternary ammonium salt **3** as the precipitate in 90% yield. In general, **3** was used without further purification. When **3** was treated with NaH in THF, 2,3,10,11-tetramethoxy-7-cyano-7,8,13,13a-tetrahydroisoindolo[1,2-b][3]benzazepine **4** was obtained as the *syn*- and *trans*-diastereoisomers[8,9], the *syn*:*trans*= 9:1 with 90% combined yield. Both the *syn*- and *trans*- diastereoisomers of **4** underwent reductive decyanation by $NaBH_4$ in EtOH to give (±)-2,3,10,11-tetramethoxy-7,8,13,13a-tetrahydroisoindolo[1,2-b][3]benzazepine (**5**)[10] in 80% yield. The structure of **5** was established with MS, ^{1}HNMR, ^{13}CNMR and C-H COSY, and the ^{1}HNMR of **5** was also compared with the ^{1}HNMR of (±)-xylopinine[11].

5 reacted with $BrCH_2CN$ in THF to give the cyanomethyl quaternary ammonium salt **6** in 60% yield as the precipitate. When **6** was treated with NaH in THF, we obtained 2,3,11,12-tetramethoxy-6-cyano-5,6,8,9,14,14a-hexahydroisoquino[1,2-b][3]benzazepine **7**[12] in 80% yield and a little amount of 2,3,11,12-tetramethoxy-8,9,14,14a-tetrahydroiso-quino[1,2-b][3]benzazepine **8**[13]. Examined by TLC and comparable experiments, **8** seemed to be formed by elimination of HCN from **7**.

The structure of **7** and **8** were determined by MS, ^{1}HNMR, ^{13}CNMR and DEPT. When treated with $NaBH_4$ in EtOH, both **7** and **8** gave the same product **9**[14]. The HRMS showed that **9** was the expected reductive decyanation product of **7**.

In conclusion, we have developed a new and convenient synthetic route to certain N-heterocycles containing the benzazepine ring. The new route provided the advantages of readily available starting materials, simple operations, high reaction selectivity as well as high yields, entailing, however, severe limitation on the substitution pattern.

References and notes

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7. Spectral data of **2:** Colorless needles from CH_3OH, m.p. 130~131°C; MS (*m/z*): 341 (M^+,50%), 165 (100%), 164 (70%); ^{1}HNMR: 2.93 (dd, 1H, *J*=10.9, 14.5 Hz), 3.25 (dd, 1H, *J*=3.8, 15.0 Hz), 3.83~4.01 (m, 15H), 4.11 (d, 1H, *J*= 14.0 Hz), 4.25 (d, 1H, *J*=11.5 Hz), 6.64 (s, 1H), 6.71 (s, 1H), 6.78 (s, 1H), 6.82 (s, 1H).
8. Spectral data of *syn*-**4 :** Colorless needles from CH_3OH, m.p. 174.0~175.0°C; MS (*m/z*): 380 (M^+, 38%), 353 (100%) ; ^{1}HNMR: 3.01 (dd, 1H, *J*=5.7, 15.0 Hz), 3.05 (dd, 1H, *J*=14.5, 9.9 Hz), 3.18 (d, 1H, *J*=14.7 Hz), 3.42 (dd, 1H, *J*=2.4, 15.0 Hz), 3.87 (br, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 3.99 (dd, 1H, *J*=3.8, 11.5 Hz), 4.16 (d, 1H, *J*=11.5 Hz), 4.34 (d, 1H, *J*=3.3 Hz), 6.74 (s, 1H), 6.81~6.82 (m, 3H); ^{13}CNMR: 39.63 (CH_2), 40.97 (CH_2), 52.90 (CH), 56.11(CH_3), 56.15 (CH_3), 56.28 (CH_3), 56.39 (CH_3), 57.59 (CH_2), 63.95 (CH), 105.65 (CH), 106.21(CH), 113.70 (CH), 115.15 (CH), 115.98 (C), 127.92 (C),

129.23 (C), 132.49 (C), 133.84 (C), 147.52 (C), 148.11(C), 148.98 (C), 149.11 (C). Anal. Calcd. for $C_{22}H_{24}N_2O_4$, C 69.46 H 6.36, N 7.36; Found: C 69.20, H 6.18, N 7.43.

9. Spectral data of *trans*-**4 :** Colorless needles from CH_3OH, m.p. 170.1~175.0°C; MS (*m/z*): 380 (M^+, 38%), 353 (100%); ^{1}HNMR: 3.13~3.21 (m, 3H), 3.45 (dd, 1H, *J*=9.6, 15.0 Hz), 3.70 (m, 1H), 3.79~3.99 (m, 14H), 4.54 (d, 1H), 6.72 (s, 1H), 6.82 (m, 3H).
10. Spectral data of **5:** Colorless needles from EtOAc, m.p. 129.5~132.0°C; MS (*m/z*): 355 (M^+); ^{1}HNMR: 2.69 (t, 1H, *J*=11.4 Hz), 2.79 (dd, 1H, *J*=5.4, 14.4 Hz), 3.09~3.21 (m, 3H), 3.32 (m, 1H), 3.45(d, 1H, *J*=8.4 Hz), 3.68 (dd, 1H, *J*=3.3, 12.3 Hz), 3.80 (dd, 1H, *J*=2.7, 13.5 Hz), 3.85~3.89 (m, 12H), 4.18 (d, 1H, *J*=12.3 Hz), 6.70 (s, 1H), 6.80 (s, 1H), 6.83 (s, 1H), 6.88 (s, 1H); ^{13}CNMR: 37.97, 41.44, 54.20, 55.52, 56.44, 56.48, 56.56, 56.70, 60.03, 69.64, 107.41, 107.83, 115.67, 115.96, 132.41, 134.30, 135.02, 137.10, 148.38, 149.83, 149.98.
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12. Spectral data of **7 :** Colorless needles from CH_3OH, m.p. 161.0~163.5°C; MS (*m/z*): 394 (M^+), 178 (100%); ^{1}HNMR: 2.79 (dd, 1H, *J*=6.1, 15.2 Hz), 2.82 (dd, 1H, *J*=2.1, 15.4 Hz), 2.83 (d, 1H, *J*=13.1Hz), 3.10 (d, 1H, *J*=15.0 Hz), 3.12 (dd, 1H, *J*=7.0, 15.4Hz), 3.20 (d, 1H, *J*=9.4 Hz), 3.23 (dd, 1H, *J*=9.8, 15.5 Hz), 3.44 (dd, 1H, *J*=3.3, 15.5 Hz), 3.67 (d, 1H, *J*=8.5 Hz), 3.88~3.94 (m, 12H), 4.05 (dd, 1H, *J*=2.1, 4.9 Hz), 6.57 (s, 1H), 6.70 (s, 1H), 6.78 (s,1H), 6.80 (s, 1H); ^{13}CNMR: 33.31 (CH_2), 36.63 (CH_2), 46.65 (CH_2), 54.17 (CH), 55.91 (CH_3), 56.15 (CH_3), 56.48 (CH_3), 57.74 (CH_2), 62.40 (CH), 110.92 (CH), 111.25 (CH), 113.33 (CH), 113.79 (CH), 116.97 (C), 123.11 (C), 129.56 (C), 132.79 (C), 133.23 (C), 147.33 (C), 147.55 (C), 148.24 (C), 148.40 (C); Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C 69.46, H 6.36, N 7.36; Found: C 69.20, H 6.18, N 7.43.
13. Spectral data of **8 :** Yellow needles from CH_3OH, m.p. 154.0~156.0°C; MS (*m/z*): 367 (M^+, 47%), 178 (100%); ^{1}HNMR: 2.10 (d, 1H, *J*=15.0 Hz), 2.61 (dd, 1H, *J*=4.9, 14.5 Hz), 3.21 (t, 1H, *J*=12.0 Hz), 3.32 (t, 1H, *J*=12.0 Hz), 3.56 (dd, 1H, *J*=0.5, 14.0 Hz), 4.52 (d, 1H, *J*=10.1Hz), 5.34 (d, 1H, *J*=7.3 Hz), 6.16 (d, 1H, *J*= 7.3 Hz), 6.48 (s, 1H), 6.57 (s, 1H), 6.64 (s, 1H), 6.94 (s, 1H); ^{13}CNMR: 38.75 (CH_2), 43.03 (CH_2), 54.99 (CH_2), 55.91 (CH_3), 56.14 (CH_3), 56.19 (CH_3), 56.55 (CH_3), 62.94 (CH), 97.48 (CH), 106.41 (CH), 110.20 (CH), 113.85 (CH), 114.17 (CH), 122.96 (C), 125.73 (C), 133.06 (C), 133.64 (C), 134.60 (C), 146.93 (C), 147.09 (C), 147.17 (C), 148.59 (C).
14. Spectral data of **9:** Colorless needles, m.p. 104.5~107.0°C; HRMS: Cacld. $C_{22}H_{27}NO_4$, 369.1940; Found: 369.1946; ^{1}HNMR: 2.86~3.53 (m, 9H), 3.66 (m, 1H), 3.83~4.03 (m, 13H), 6.6~6.8 (m, 4H).

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