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Ring Enlargement of Alkaloids

Yu Xin LIU, Shu Feng CHEN[#], Xiao Tian LIANG*

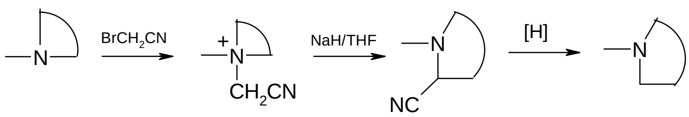
Institute of Materia Medica, Chinese Academy of Medical Science
& Peking Union Medical College, Beijing 100050

Abstract: The procedure for the ring enlargement of N-heterocycles with the net result of CH_2 insertion was successfully carried out with certain alkaloids such as tetrahydroberberine and strychnine.

Keywords: Ring enlargement, alkaloids, reductive decyanation.

Previous publications[1] from our laboratory had reported the ring enlargement reaction of quaternary ammonium salts of N-methyl-tetrahydroisoquinoline followed by reductive decyanation with the net result of the insertion of an extra CH_2 group , as shown in **Scheme I**.

Scheme I



The methodology failed with some naturally occurring alkaloids such as cephalotaxine and atropine[2]. One reason is that some of the quaternary ammonium salts are difficult to prepare, the other one is that some of the quaternary ammonium salts underwent Hofmann elimination or Sommelet rearrangement[2]. But when we tested it with certain kinds of alkaloids such as strychnine and tetrahydroberberine, satisfactory results were obtained. Here we report some of our results.

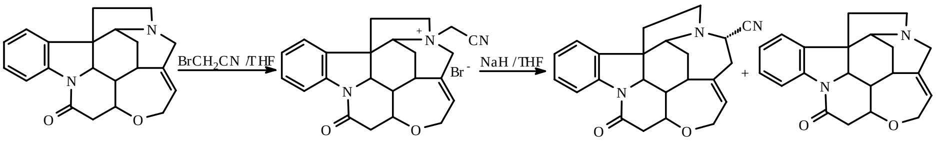
Results and Discussion

The first example came from strychnine **(1)**. As shown in **Scheme II** , strychnine reacted with bromoacetonitrile to give its quaternary ammonium salt **2** in 100% yield.

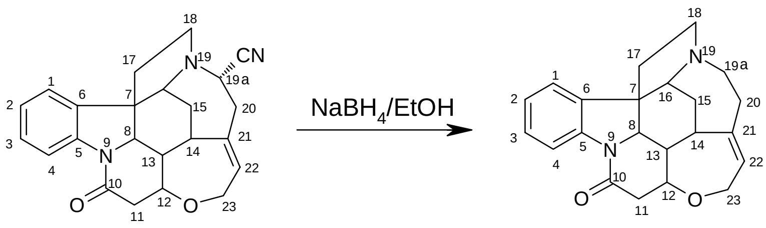
[#] Deceased

When **2** was treated with NaH in anhydrous THF at 50℃ for 8 hours, it gave two major and three minor products (observed by TLC). The two major products were isolated and characterized as **3**[3] in 70% yield and the original alkaloid **1** by decyanomethylation in 10% yield. The three minor products were difficult to be isolated and the structures were not determined yet. When **3** was treated with $NaBH_4$ in ethanol, it gave reductive decyano product **4**[4] in 88% yield.

Scheme II



1 **2** **3** **1**

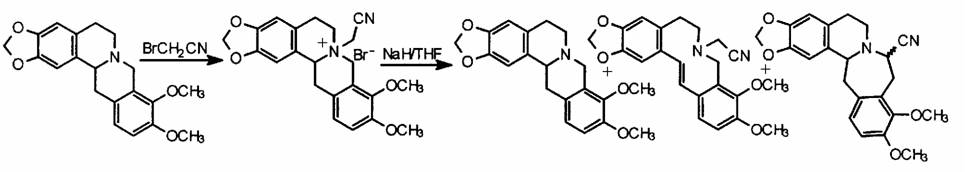


3 **4**

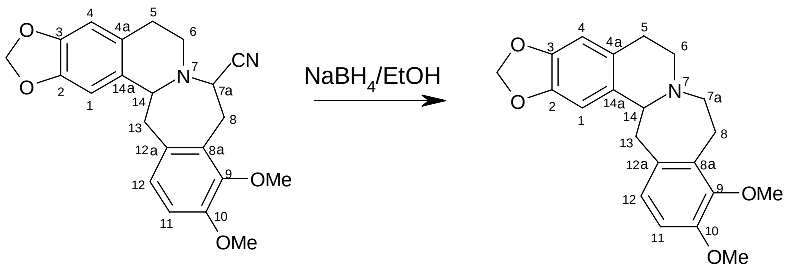
The site of homologation and the α-configuration of the CN group in **3** were established by 1D and 2D NMR, including DIFNOE. It is seen that the ring enlargement involves the migration of an allylic group.

The second example came from (±)-tetrahydroberberine **5**. As shown in **scheme III**, **5** reacted with bromoacetonitrile to give its quaternary ammonium salt **6** in 80% yield. When **6** was treated with NaH in anhydrous THF at 50℃ for 10 hours, it gave **8**[5] as the ring enlargement products in 40% yield, and **7**[6] as the Hofmann elimination product in 25% yield, and **5** in 10% yield. ^{1}HNMR and ^{13}CNMR showed that **8** existed as one of the two possible diasteromers in pure form. By examination of the molecular model with favourable conformation for rearrangement, the enantiomeric pair of (7aR,14R) and (7aS,14S) is perferable. When **8** was treated with $NaBH_4$ in ethanol, it gave the reductive decyano product **9**[7] in 90% yield.

Scheme III



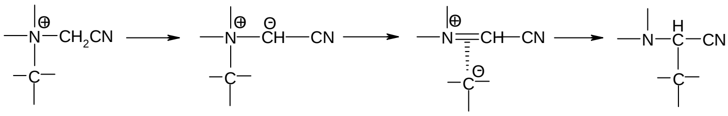
5 **6** **5** **7** **8**



8 **9**

In the case of **6**, there are two benzylic groups on nitrogen as candidates for migration. Incipient rupture of the N-C bond of ylide **11** gives **12**, where the migrant has some anionic character, which is better accommodated by the benzylic group with fewer electron-donating substituents.

Scheme IV



10 **11** **12** **13**

Experimental

General procedure for the preparation of quaternary ammonium salts. To the solution of the alkaloid (0.5 mmol) in anhydrous THF (20 ml) was added bromoacetonitrile (0.1 ml, 1.6 mmol). The reaction mixture was refluxed until complete consumption of the alkaloid. Then the precipitate was filtered and washed with anhydrous THF, dried, and used without further purification.

General procedure for ring enlargement . To a 100ml flask was added quaternary ammonium salt (0.1 mmol), NaH (24 mg, 1 mmol) and anhydrous THF (50 ml), the reaction mixture was stirred and heated at 50℃ for 8 hrs. The mixture was filtered and the filtrate was concentrated to dryness, the residue was separated by chromatography.

General procedure for reductive decyanation. To the solution of α-nitrile (0.1mmol) in anhydrous EtOH (100 ml) was added $NaBH_4$ (38 mg, 1 mmol) in portions, followed by stirring for 2 hrs at 25℃ and 5 hrs at 50℃. Then the EtOH was evaporated under reduced pressure, and the residue was separated by chromatography.

References and notes

1. X.T. Liang, *et al*, *J. Chin. Chem. Soc.*, **1995**, *42*, 601.
2. J.W. Zhang, Ph.D. Thesis, Institute of Materia Medica, CAMS&PUMC, Beijing, 1996.
3. Spectral data of **3**: m.p. 263~265℃ (colourless crystals from CH_3OH); MS (m/z): 373 (M^+); ^{1}HNMR (500 MHz, $CDCl_3$): δ1.41 (ddd, 1H, *J*=4.4, 4.9, 10.4 Hz, C_{13}-H), 1.70 (dd, 1H, *J*=3.3, 15.3 Hz, C_{15}-H), 1.82 (ddd, 1H, *J*=4.8, 13.0, 13.4 Hz, C_{17}-H), 2.25 (ddd, 1H, *J*=5.3, 9.0, 13.4 Hz, C_{17}-H), 2.42 (dt, 1H, *J*=4.0, 15.3 Hz, C_{15}-H), 2.67 (dd, 1H, *J*=5.2, 16.2 Hz, $C_{11\beta}$-H), 2.72

(dd, 1H, J=10.5, 13.9 Hz, $C_{20\alpha}$-H), 2.90 (ddd, 1H, J=5.3, 13.0, 13.6 Hz, $C_{18\beta}$-H), 2.93 (dd, 1H, J=3.3, 4.4 Hz, C_{14}-H), 2.97 (dd, 1H, J=8.0, 13.9 Hz, $C_{20\beta}$-H), 3.06 (ddd, 1H, J=4.8, 8.8, 13.6 Hz, $C_{18\alpha}$-H), 3.11 (dd, 1H, J=8.3, 16.2 Hz, $C_{11\alpha}$-H), 3.40 (d, 1H, J=4.4 Hz, C_{16}-H), 3.94 (dd, 1H, J=8.0, 10.5 Hz, C_{19a}-H), 4.0 (dt, 1H, J=2.2, 14.8 Hz, $C_{23\beta}$-H), 4.06 (d, 1H, J=10.4 Hz, C_8-H), 4.16 (ddd, 1H, J=4.9, 5.2, 8.3 Hz, C_{12}-H), 4.21 (dd, 1H, J=7.0, 14.9 Hz, $C_{23\alpha}$-H), 5.71 (br, 1H, C_{22}-H), 7.10 (dd, 1H, J=7.1, 7.4 Hz, C_2-H), 7.20 (d, 1H, J=7.1 Hz, C_1-H), 7.27 (dd, 1H, J=7.4, 8.1 Hz, C_3-H), 8.08 (d, 1H, J=8.1 Hz, C_4-H) ; ^{13}CNMR (125 MHz, $CDCl_3$): 28.67 (C_{15}), 34.91 (C_{14}), 40.12 (C_{17}), 41.29 (C_{20}), 41.69 (C_{11}), 48.05 (C_{18}), 48.09 (C_{13}), 48.87 (C_{19a}), 53.26 (C_7), 59.71 (C_{16}), 63.34 (C_8), 66.36 (C_{23}), 78.58 (C_{12}), 116.26 (C_4), 117.43 (-CN), 122.51 (C_2), 124.47 (C_1), 127.19 (C_{22}), 128.70 (C_3), 131.77 (C_6), 140.93 (C_{21}), 142.63 (C_5), 170.15 (C_{10}).

4. Spectral data of **4**: m.p. 250℃ (colourless crystals from CH_3OH) ; MS(m/z): 348(M^+); ^{1}HNMR (500 MHz, $CDCl_3$): 1.47 (ddd, 1H, J=4.7, 4.9, 11.1 Hz, C_{13}-H), 1.70 (dt, 1H, J=3.9, 15.4 Hz, C_{15}-H), 1.91 (m, 2H, C_{17}-H), 2.45 (dt, 1H, J=7.6, 15.1 Hz, C_{20}-H), 2.58 (dt, 1H, J=7.4, 15.1 Hz, C_{20}-H), 2.67 (dt, 1H, J=2.9, 15.4 Hz, C_{15}-H), 2.73 (dd, 1H, J=5.0, 16.5 Hz, C_{11}-H), 2.80 (br, 1H, C_{14}-H), 3.04 (dd, 1H, J= 8.0, 16.6 Hz, C_{11}-H), 3.07 (dt, J=5.5, 12.1 Hz, C_{18}-H), 3.17 (dt, 1H, J=8.0, 12.1 Hz, C_{18}-H), 3.24 (dd, 1H, J=7.2, 17.2 Hz, C_{19a}-H), 3.69 (dt, 1H, J=6.9, 12.2 Hz, C_{23}-H), 3.80 (d, 1H, J=11.1 Hz, C_8-H), 3.90 (dbr, 1H, J=17.1 Hz, C_{19a}-H), 4.10 (m, 2H, C_{16}-H, C_{12}-H), 5.56 (d, 1H, J=6.6 Hz, C_{22}-H), 7.10 (dd, 1H, J=7.2, 7.8 Hz, C_3-H), 7.24 (t, 2H, C_1-H, C_2-H), 8.10 (d, 1H, J=7.8 Hz, C_4-H); ^{13}CNMR (125 MHz, $CDCl_3$): 29.27 (C_{15}), 39.24 C_{20}), 39.60 (C_{14}), 41.43 (C_{11}), 42.19 (C_{12}), 116.03 (C_4), 122.14 (C_2), 124.24 (C_1), 127.52 (C_{22}), 128.51 (C_3), 133.48 (C_6), 138.42 (C_{21}), 141.40 (C_5), 170.06 (C_{10}).

5. Spectral data of **7**: m.p. 209.5℃ (colourless needles from CH_3OH); MS (m/z): 378(M+), 348, 164; ^{1}HNMR (500 MHz, $CDCl_3$): 2.74 (s, 2H, $-CH_2-$), 3.0 (br, 2H, $-CH_2$-N), 3.55 (s, 2H, $-NCH_2$-Ar), 3.89 (m, 8H, 2-OCH_3 +-NCH_2CN), 5.95 (s, 2H, $-OCH_2O-$), 6.52 (d, 1H, J=15.8 Hz, CH=CH), 6.65 (s, 1H, Ar-H), 6.87 (d, 1H, J=8.5 Hz, Ar-H), 7.00 (d, 1H, J=8.5 Hz, Ar-H), 7.20 (d, 1H, J=15.8 Hz, CH=CH).

6. Spectral data of **8**: m.p. 204.0℃, 209.5℃ (colourless needles from CH_3OH); MS (m/z): 378 (M^+), 377, 351, 176, 161; ^{1}HNMR (500 MHz, $CDCl_3$+D_2O)*: 2.61 (dd, 1H, J=5.7, 14.7 Hz, C_5-H), 2.84 (td, 1H, J=3.0, 10.9 Hz, C_6-H), 2.95 (br, 1H, C_6-H), 3.04 (br, H, C_8-H), 3.08 (m, 2H, C_5-H, C_{13}-H), 3.15 (dd, 1H, J=8.7, 15.1 Hz, C_8-H), 3.73 (dd, 1H, J=6.2, 15.0 Hz, C_{13}-H), 3.83 (br, 1H, C_{7a}-H), 3.87 (s, 3H, $-OCH_3$), 3.89 (s, 3H, $-OCH_3$), 4.27 (dd, 1H, J=1.9, 6.2 Hz, C_{14}-H), 5.93 (s, 2H, $-OCH_2O-$), 6.54 (s, 1H, C_3-H), 6.76 (s, 1H, C_1-H), 6.78 (d, 1H, J=8.2 Hz, C_{11}-H), 6.96 (d, 1H, J=8.2 Hz, C_{12}-H); ^{13}CNMR (125 MHz, $CDCl_3$): 30.06 (C_5), 30.20 (C_8), 45.99 (C_{13}), 51.72 (C_6), 55.74 (C_{10}-OCH_3), 57.70 (C_{7a}), 61.04 (C_9-OCH_3), 61.26 (C_{14}), 100.95 ($-OCH_2O-$), 107.07 (C_1), 107.99 (C_4), 111.01 (C_{11}), 118.26 (-CN), 124.15 (C_{12}), 127.89 (C_{8a}), 129.48 (C_{12a}), 131.04 (C_{14a}), 134.10 (C_{4a}), 146.05 (C_2), 146.37 (C_3), 147.50 (C_{10}), 151.57 (C_9).

   * D_2O was used to remove any spurious acids in the $CDCl_3$ solvent, in order to avoid the appearance of blurred ^{1}H signals in the high field region.

7. Spectral data of **9**: m.p. 148.5~149.5℃ (colourless needles from CH_3OH); MS(m/z): 353 (M^+); ^{1}HNMR (500 MHz, $CDCl_3$): 2.62~2.79 (m, 6H), 3.21~3.28 (m, 3H), 3.50 (dd, 1H, J=9.3, 15.1 Hz), 3.76 (s, 3H, $-OCH_3$), 3.80 (dd, 1H, J=3.7, 8.8 Hz), 3.86 (s, 3H, $-OCH_3$), 5.91 (s, 2H, $-OCH_2O-$), 6.54 (s, 1H, Ar-H), 6.70 (s, 1H, Ar-H), 6.71 (d, 1H, J=8.2 Hz, Ar-H), 6.93 (d, 1H, J=8.2 Hz, Ar-H); ^{13}CNMR (125 MHz, $CDCl_3$): 25.06 (C_8), 29.60 (C_5), 42.83 (C_{13}), 48.30 (C_6), 55.77 (C_{10}-OCH_3), 56.92 (C_{7a}), 60.96 (C_9-OCH_3), 63.58 (C_{14}-H), 100.70 ($-OCH_2O-$), 107.05 (C_1), 108.19 (C_4), 109.52 (C_{11}), 124.41(C_{12}), 127.95 (C_{8a}), 132.36 (C_{12a}), 134.74 (C_{4a}), 136.04 (C_{14a}), 145.91 (C_2), 145.91 (C_3), 146.44 (C_{10}), 151.33 (C_9).

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