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An unexpected rearrangement of the benzofurobenzazepine skeleton of galanthamine-type alkaloids

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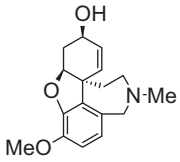
ABSTRACT

Attempted cyclisation of N-methylated spiro benzazepine–cyclohexenone (**5**) into the corresponding *N*-methyl tetracyclic unit of galanthamine-type alkaloids (**6**) instead gave an unexpected rearrangement to yield a cyclopentanoisoquinolinone derivative (**7**). Methylation of the tetrahydrobenzofurobenzazepine tetracycle resulted in the expected *N*-methyl derivative **6**, and the anomalous product **8**, with structure similar to that of **7**.

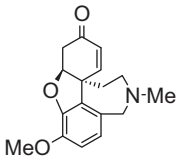
(−)-Galanthamine (**1**) is an *Amaryllidaceae* alkaloid,[1] isolated from the flowers and bulbs of the Caucasian snowdrop (*Galanthus woronowii*), and exhibits competitive and reversible acetylcholine esterase (AChE) inhibition. Moreover, this molecule displays allosteric potentiation of neuronal nicotinic receptors for acetylcholine.[2] (−)-Galanthamine hydrobromide (Razadyne, Reminyl) enhances significantly cognitive functions and is used for the treatment of mild to moderate Alzheimer's disease.[3,4]

A number of synthetic routes have been elaborated[1] for the preparation of (−)-galanthamine using different key steps to form the tetracyclic ring system characteristic of galanthamine-type *Amaryllidaceae* alkaloids.[5–9] Most synthetic strategies utilized a biomimetic approach via intramolecular phenolic oxidative coupling to install the quaternary spiro carbon. In relation to this type of synthetic processes, narwedine (**2**) as well as its biogenetic precursor[10] can be considered the most important intermediates.

Recently,[11] we succeeded in synthesizing the hexahydrobenzofurobenzazepine trione **3** which represents the appropriate key intermediate for the preparation of the demethoxy derivative of narwedine (**2**). The synthesis of compound **3** was achieved starting from spirocyclohexenone derivative **4** in one step via demethylation of the methoxy group and cyclisation using methanesulfonic acid in the presence of methionine.[11]



1



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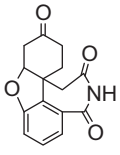

3

The spiro compound **4**[11,12] was N-methylated with methyl iodide in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme 1) giving *N*-methyl derivative **5** in 53% yield. Next, the cyclisation reaction was performed like that used for the preparation of tetracycle **3**. Compound **5** was allowed to react in methanesulfonic acid in the presence of racemic methionine at room temperature for several hours. After work-up, however, the *N*-methyl tetracycle **6** was not isolated, but instead the unexpected cyclopentanoisoquinolinone derivative **7** was obtained. This type of tricyclic dione is unknown in the literature.

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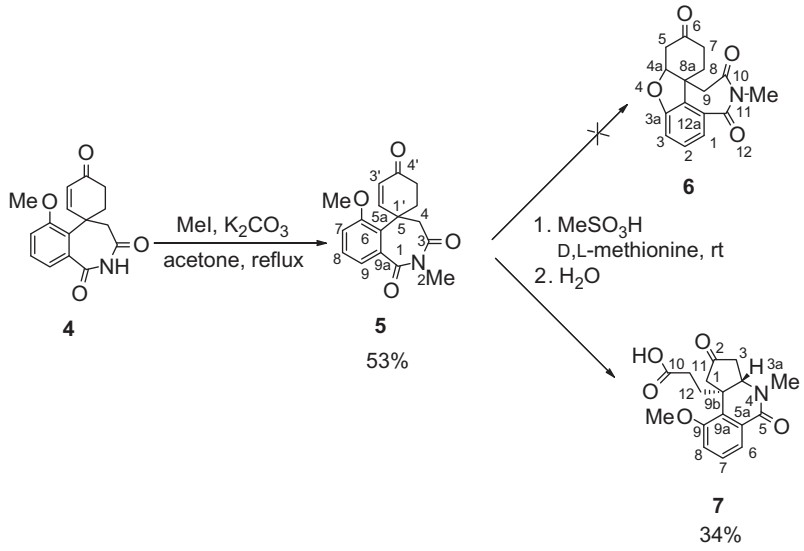
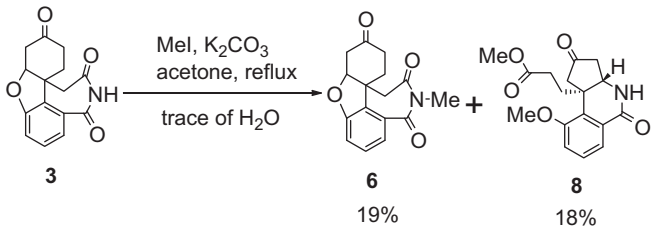


Scheme 1.

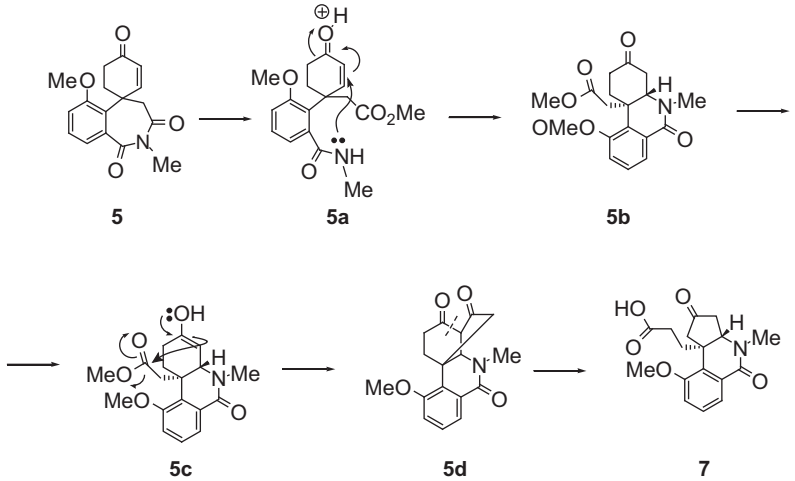
Our next attempt to obtain the target molecule was to allow the hexahydrobenzofurobenzazepine tetracycle **3** to react with methyl iodide so as to prepare the *N*-methyl imide **6**. The reaction conditions in this procedure were the same as those used for the methylation of spiro derivative **4** (Scheme 2).

In this reaction two products were isolated: the expected *N*-methyl tetracycle **6** was obtained in 19% yield, and surprisingly, as in the previously attempted cyclisation reaction, the analogous tricyclic cyclopentanoisoquinoline dione **8** was also obtained.

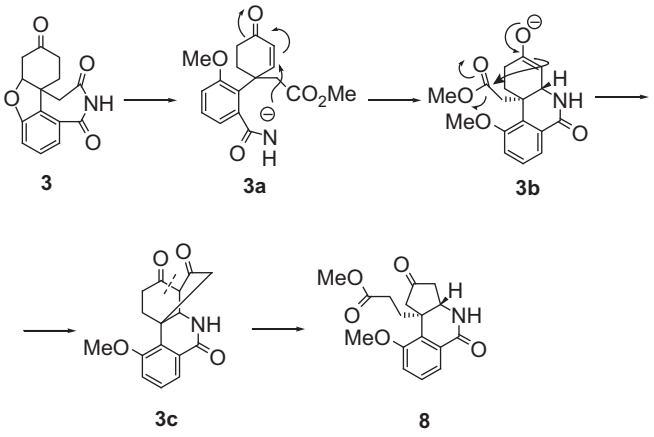


Scheme 2.

High-resolution mass spectrometric data indicated that compound **7**[13] had the elementary composition $C_{17}H_{19}NO_5$ (as opposed to $C_{16}H_{15}NO_4$ for compound **6**). In the ^1H NMR spectra, one of the most conspicuous differences between **7** and **6** is a doublet of doublets signal belonging to a CH methine proton at 4.10 ppm in the ^1H spectrum of **7** instead of the expected triplet signal at 4.90 ppm due to H-4a as for **6**. The corresponding carbon signal in **7** occurred at 62.7 ppm, (86.5 ppm in **6**). These chemical shifts indicate that this methine is situated next to a nitrogen instead of an oxygen atom. In addition, the $-CH_2-C(O)-CH_2-$ ketone carbon signal was shifted downfield by 4.5 ppm in the ^{13}C spectrum of **7** compared to **6**, suggesting that this carbonyl group is in a strained five-membered ring. There was a singlet at 3.84 ppm in the ^1H spectrum of **7** due to an additional *O*-methyl group connected to the aromatic ring. A broad singlet at 12.0 ppm, not connected to a carbon, was likely to belong to a carboxylic acid OH. From a structurally informative point of view, the 2D ^1H–^1H correlation spectrum showed a connection between the CH signal at 4.10 ppm (H-3a) and the diastereotopic CH_2 signals at 1.94 and 2.86 ppm (CH_2-3), and also between the CH_2 signals at 1.94–1.98 and 2.13–2.18 ppm (CH_2-11) and 2.00–2.05 and 2.22–2.26 ppm (CH_2-12). These data, together with further ^1H–^1H, direct ^1H–^{13}C, and long-range



Scheme 3.



Scheme 4.

^{1}H–^{13}C scalar connectivities as measured from 2D experiments, allowed the unambiguous determination of the structure of **7** as shown in Scheme 2. The ^{1}H and ^{13}C assignments derived from, and supported by, the 2D scalar correlation experiments are provided.[13] The relative configuration of C(3a) and C(9b) follows from the fact that the measured vicinal $J_{3a,3\beta}$ = 8.1 Hz and $J_{3a,3\alpha}$ = 10.6 Hz couplings are only consistent with the *trans* geometry of the ring fusion.

The structural elucidation of compound **8**[14] (Scheme 2) rests on an entirely analogous procedure and argument as discussed for compound **7**.

The rearrangement yielding compounds **7** and **8** may be plausibly rationalized in terms of the mechanisms shown for an acidic medium in Scheme 3, and for a basic medium in Scheme 4.

In the latter case, cleavage of the ether bond provides a phenol which is subsequently methylated, and in addition a cyclohexenone is formed. After conjugate addition of the nitrogen atom on the enone, Claisen condensation occurs between the cyclohexanone methylene group and the ester group. Subsequently, a retro-Claisen condensation forms the cyclopentanone ring and the side chain, yielding the cyclopentanoisoquinoline **8**.

To sum up, we may conclude that in the course of an attempted cyclisation of compound (**5**) into a unit of galanthamine-type alkaloids (**6**) an unexpected rearrangement occurred to yield a new derivative (**7**). Subsequent methylation resulted in the expected derivative **6**, and the anomalous product **8**.

Acknowledgements

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References and notes

1. Marco-Contelles, J.; Carreiras, M. D.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116.
2. Maelicke, A.; Samochocki, M.; Jostock, R.; Fehrenbacher, A.; Ludwig, J.; Albuquerque, E. X.; Zerlin, M. *Biol. Psychiatry* **2001**, *49*, 279.
3. Weinstock, M. *CNS Drugs* **1999**, *12*, 307.
4. Blesa, R.; Davidson, M.; Kurz, A.; Reichman, W.; van Baelen, B.; Schwalen, S. *Dementia Geriatr. Cogn. Disord.* **2003**, *15*, 79.
5. Czollner, L.; Frantsist, W.; Küenburg, B.; Hedenig, U.; Fröhlich, J.; Jordis, U. *Tetrahedron Lett.* **1988**, *39*, 2087.
6. Czollner, L.; Treu, M.; Fröhlich, J.; Küenburg, B.; Jordis, U. *ARKIVOC* **2001**, *i*, 191.
7. Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
8. Satcharoen, V.; McLean, N. J.; Kemp, S. C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867.
9. Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498.
10. Eichhorn, J.; Takada, T.; Kita, Y.; Zenk, M. H. *Phytochemistry* **1998**, *49*, 1037.
11. Herke, K.; Hazai, L.; Hudák, M. Sz.; Ábrahám, J.; Sánta, Zs.; Háda, V.; Szántay, Cs., Jr.; Szántay, Cs. *ARKIVOC* **2009**, *xi*, 235.
12. Gorka, Á.; Hazai, L.; Szántay, Cs., Jr.; Háda, V.; Szabó, L.; Szántay, Cs. *Heterocycles* **2005**, *65*, 1359.
13. *Spectral data are as follows for compound* **7**. IR (KBr): 3436, 2929, 1747, 1641, 1277, 1256, 820, 755 cm^{-1}. ^{1}H NMR, (800 MHz, DMSO-d_6): 1.94 (ddd, 1H, J_{gem} = 18.6 Hz, $J_{3\alpha,3a}$ = 10.6 Hz, $J_{3\alpha,1\alpha}$ = 2.2 Hz, H_α-3), 1.94–1.98 (m, 1H, H_x-11), 2.00–2.05 (m, 1H, H_x-12), 2.13–2.18 (m, 1H, H_y-11), 2.22–2.26 (m, 1H, H_y-12), 2.60 (dd, 1H, J_{gem} = 18.5 Hz, $J_{1\beta,3\beta}$ = 1.3 Hz, H_β-1), 2.86 (ddt, 1H, J_{gem} = 18.6 Hz, $J_{3\beta,3a}$ = 8.1 Hz, $J_{3\beta,1\alpha;\ 3\beta,1\beta}$ = 1.3 Hz, H_β-3), 3.57 (ddd, 1H, J_{gem} = 18.5 Hz, $J_{1\alpha,3\alpha}$ = 2.2 Hz, $J_{1\alpha,3\beta}$ = 1.3 Hz, H_α-1), 3.04 (s, 3H, NCH_3), 3.84 (s, 3H, CH_3O), 4.10 (dd, 1H, $J_{3a,3\alpha}$ = 10.6 Hz, $J_{3a,3\beta}$ = 8.1 Hz, H_β-3a), 7.26 (dd, 1H, $J_{8,7}$ = 8.3 Hz, $J_{8,6}$ = 1.2 Hz, H-8), 7.40 (dd, 1H, $J_{7,8}$ = 8.3 Hz, $J_{7,6}$ = 7.8 Hz, H-7), 7.64 (dd, 1H, $J_{6,7}$ = 7.8 Hz, $J_{6,8}$ = 1.2 Hz, H-6), 12.0 (br s, 1H, H–COOH). ^{13}C NMR (200 MHz, DMSO-d_6): 29.8 (C-11), 33.8 (C-12), 33.9 (NCH_3), 43.1 (C-3), 44.4 (C-9b); 49.5 (C-1), 55.7 (OCH_3), 62.7 (C-3a), 115.9 (C-8), 120.3 (C-6), 126.6 (C-9a), 128.5 (C-7), 130.2 (C-5a), 157.3 (C-9), 161.6 (C-5), 174.0 (C-10), 212.6 (C-2) ppm. MS (ESI): *M*+H: *m*/*z* 318.13320, calcd value for $C_{17}H_{20}NO_5$: 318.13360 (Δ: −1.2 ppm). MS^2 of *m*/*z* 318: *m*/*z* 300 (100), 258 (2).
14. *Spectral data are as follows for compound* **8**. IR (KBr): 3409, 1745, 1733, 1671, 1261, 1053, 758 cm^{-1}. ^{1}H NMR (800 MHz, DMSO-d_6): 2.01–2.10 (m, 3H, H_x-11, H_x-12, H_α-3), 2.26–2.30 (m, 1H, H_y-12), 2.35–2.39 (m, 1H, H_y-11), 2.58 (dd, 1H, J_{gem} = 18.5 Hz, $J_{1\beta,3\beta}$ = 1.2 Hz, H_β-1), 2.62 (ddt, 1H, J_{gem} = 18.5 Hz, $J_{3\beta,3a}$ = 8.0 Hz, $J_{3\beta,1\beta}$ = 1.2 Hz, H_β-3), 3.46 (dd, 1H, J_{gem} = 18.5 Hz, $J_{1\alpha,3\alpha}$ = 2.0 Hz, H_α-1), 3.51 (s, 3H, C(10)–OCH_3), 3.83 (s, 3H, C(9)–OCH_3), 4.02 (ddd, 1H, $J_{3a,3\alpha}$ = 10.2 Hz, $J_{3a,3\beta}$ = 8.0 Hz, $J_{3a,4}$ = 4.9 Hz, H_β-3a), 7.25 (dd, 1H, $J_{8,7}$ = 8.3 Hz, $J_{8,6}$ = 1.2 Hz, H-8), 7.39 (dd, 1H, $J_{7,8}$ = 8.3 Hz, $J_{7,6}$ = 7.7 Hz, H-7), 7.61 (dd, 1H, $J_{6,7}$ = 7.7 Hz, $J_{6,8}$ = 1.2 Hz, H-6), 8.28 (d, 1H, $J_{4,3a}$ = 4.9 Hz, H-4). ^{13}C NMR (200 MHz, DMSO-d_6): 29.7 (C-11), 33.3 (C-12), 44.1 (C-9b), 45.4 (C-3), 49.2 (C-1), 51.3 (C(10)–OCH_3), 55.0 (C-3a), 55.7 (C(9)–OCH_3), 116.1 (C-8), 120.1 (C-6), 127.3 (C-9a), 128.4 (C-7), 130.2 (C-5a), 157.5 (C-9), 162.9 (C-5), 172.9 (C-10), 213.2 (C-2). MS (ESI): *M*+H: *m*/*z* 318.13320, calcd value for $C_{17}H_{20}NO_5$: 318.13360 (Δ: −1.3 ppm). MS^2 of *m*/*z* 318: *m*/*z* 286 (100), 244 (4).