Pergamon

Tetrahedron Letters 43 (2002) 869–872

TETRAHEDRON LETTERS

A novel rearrangement in the acid-catalyzed *O*-demethylation of a 6,14-*endo*-ethenotetrahydrothebaine using hydrobromic acid†

Yibin Zeng,[a,‡] Jie Yang,[a,‡] Zhuibai Qiu,[a,*] Jian Cheng,[b] Chunhua Hu[b] and Peiju Zhen[b]

[a]*Department of Medicinal Chemistry, School of Pharmacy, Shanghai Medical University (Now Fudan University), 200032 Shanghai, PR China*

[b]*Research Center of Analysis & Measurement, Fudan University, 200433 Shanghai, PR China*

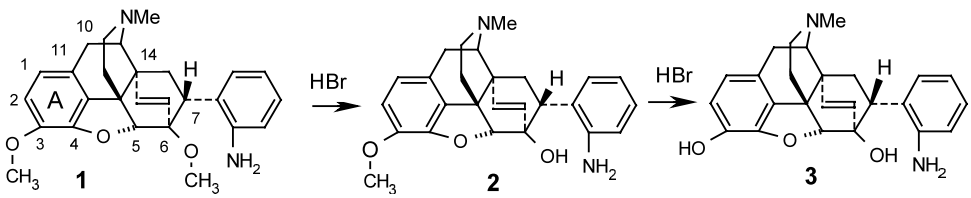
Received 16 October 2001; revised 19 November 2001; accepted 30 November 2001

Abstract—A new rearrangement byproduct, 3-methyl-1,2,3,4,4a,4b,9a,15,15a,15b-decahydro-(4,5);(4a,15)-dimethanotricyclo-(4,3,1,$0^{2,7}$)deca[8,9,1,10-a,b,c]pyrido[4,3-a]-acridin-6-en-9-ol-8-one, has been isolated from the acid-catalyzed *O*-demethylation of 7α-*o*-aminophenyl-6,14-*endo*-ethenotetrahydrothebaine. The mechanism of its formation involving a novel annulation of the 6,14-*endo*-ethenylene moiety with the A ring aromatic carbons is discussed.

During our investigation of the *O*-demethylation of 7α-*o*-aminophenyl-6,14-*endo*-ethenotetrahydrothebaine (**1**)[1,2] using hydrobromic acid it was found that at room temperature, after 10 h, a 6-demethylated compound (**2**) could be isolated, but a considerable amount of starting material remained; when the temperature was raised above 100°C (120–130°C, oil bath) and the reaction time prolonged (20 h), the 3,6-didemethylated compound (**3**) became the major product (Scheme 1). This is consistent with Bentley's previous studies on the *O*-demethylation of 7-substituted 6,14-*endo*-ethenotetrahydrothebaines using hydrobromic acid.[3–5]

It is interesting to note that in the later process with increased reaction temperature and time, we also isolated a new compound (**4**) (18%)[6] with a molecular weight of 384 (M^+) whose structure could not be characterized according to the previously known acid-catalyzed rearrangements of 6,14-*endo*-ethenotetrahydrothebaines. There were twenty five carbon signals in the ^{13}C NMR (DMSO-d_6) spectrum: (198.51, 174.70, 158.32, 143.45, 130.69, 127.66, 127.58, 126.22, 125.36, 123.91, 84.66, 66.55, 65.18, 61.17, 59.49, 56.59, 51.84, 47.65, 46.13, 44.04, 40.13, 38.44, 31.07, 28.07, 27.08). Among them, 15 were sp^3 carbons: four quaternary, six tertiary, four secondary and one primary (which were identified by DEPT); and ten were sp^2 carbons, two of which were connected with a heteroatom (O or N). C8 (C=O) and C9b (C=N) were correlated with the two most downfield signals (198.51, 174.70). IR also indicated the presence of a C=O absorption at 1660 cm^{-1} and an OH absorption at 3440 cm^{-1}.

It was decided to obtain crystals for X-ray crystallographic analysis. A crystal with dimension of 0.3×0.4×0.5 mm of compound **4** was obtained after 24 h crystallization from anhydrous ethanol and mounted on an Enraf-Nonius CAD4 diffractometer with



Scheme 1.

Keywords: *O*-demethylation; 6,14-*endo*-ethenotetrahydrothebaine.

* Corresponding author. Fax: 86-21-64039987; e-mail: zbqiu@shmu.edu.cn

† See Ref. 1.

‡ Present address: Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, USA.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02283-3

graphite-monochromatized Mo Kα radiation ($\lambda=0.71073$ Å) for collection of intensity data by using the $\omega/2\theta$ scan technique ($0\leq 2\theta\leq 52°$). A total of 2166 reflections were measured and 1428 observed reflections with $I>3\sigma(I)$ were used for structure determination. The data were corrected for LP factors and for empirical absorption. The crystal structure was determined by direct methods (MULTAN-82). The refinement of positional anisotropic thermal parameters was carried out by the full-matrix least-squares method to final structural refinement converged with unweighted and weighted ($\omega=1$) R factors of 0.048 and 0.051, respectively. The maximum peak in the final difference Fourier map is 0.23 e Å^{-3}. $S=1.18$, $(\Delta/\sigma)_{max}=0.01$. The structure of compound **4** was determined as: 3-methyl-1,2,3,4,4a,4b,9a,15,15a,15b-decahydro-(4,5);(4a,15) - dimethanotricyclo(4,3,1,$0^{2,7}$)deca[8,9,1,10 - a,b,c]-pyrido[4,3-a]-acridin-6-en-9-ol-8-one (Fig. 1), which correlated well with its ^{1}H NMR spectrum (DMSO-d_6) 10.95 (br, 1 H, C9-OH), 7.52–7.15 (m, 5 H, C11-H, C12-H, C13-H, C14-H, C6-H), 6.35 (d, 1 H, C7-H, $J_{6,7}=9.6$ Hz), 4.15 (d, 1 H, C9a-H, $J=10.6$ Hz), 3.65 (m, 1 H, C15a-H), 3.52–3.35 (m, 3 H, C15-H, C4-H, C2eq-H), 3.32–3.15 (m, 2 H, C2ax-H, C18β-H), 3.05 (s, 1 H, C16-H), 2.90 (dd, 1 H, C17β-H, $J_{17\alpha,17\beta}=14.5$ Hz, $J_{17\beta,15\beta}=9.7$ Hz), 2.70 (s, 3 H, N-CH_3), 2.55–2.20 (m, 3 H, C4b-H, C18a-H, C1ax-H), 1.80 (d, 1 H, C1eq-H), 1.45 (dd, 1 H, C17α-H, $J_{17\alpha,17\beta}=14.5$ Hz, $J_{17\alpha,15\beta}=7$ Hz) and the ^{13}C NMR data as well.

To our knowledge annulation of the 6,14-*endo*-ethenylene moiety of a 6,14-*endo*-ethenotetrahydrothebaine with A ring aromatic carbons has not been observed in previous studies of acid-catalyzed rearrangements.

Regarding the possible pathway of formation of this novel product, it can be rationalized on the basis of the following mechanism (Scheme 2): in the acidic medium, the 6-demethylated intermediate **2** could undergo rearrangement by opening the C5-bridge-dihydrofuran ring with migration of C7 to give the C6-one **5**.[4,5] A second demethylation at C3 and annulation of the 6,14-*endo*-ethenylene moiety of the intermediate **6** with the A ring cation generated under the acidic conditions would then give the bridged ketone intermediate **7**. Final condensation of the C6-carbonyl and the adjacent *ortho*-aminophenyl group would afford the imine **4**.

During monitoring the reaction by TLC, we noticed that there was another spot before the appearance of compound **4**, which diminished with the production of **4**. We thought that it could be due to the intermediate

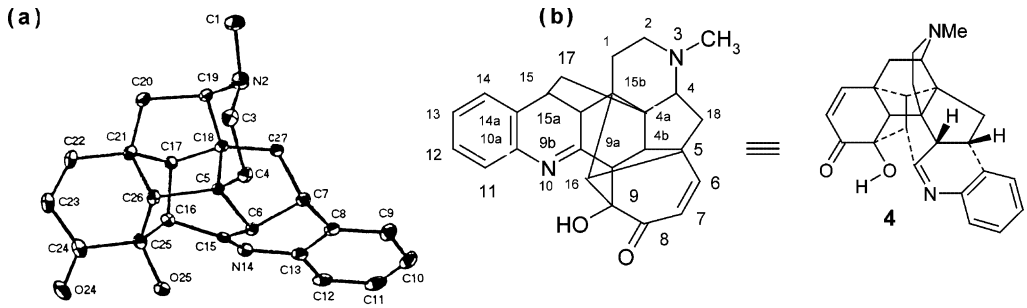
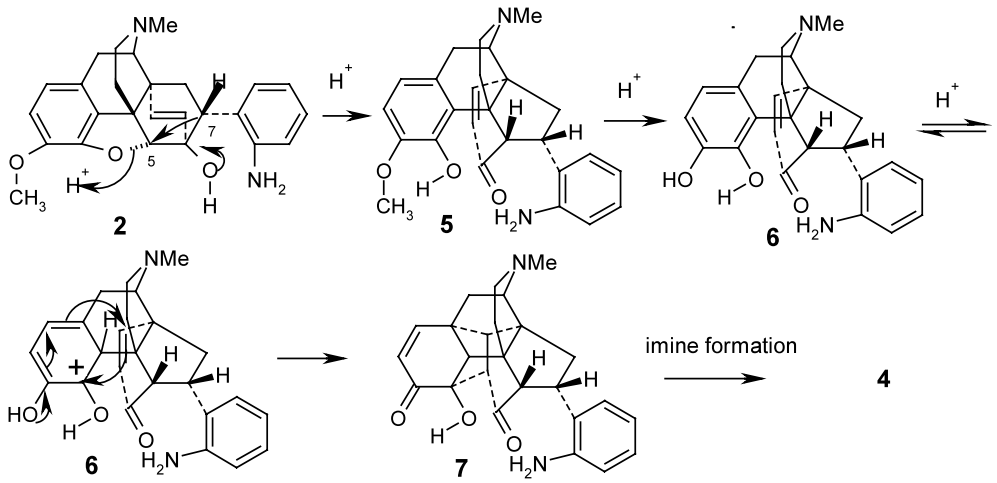
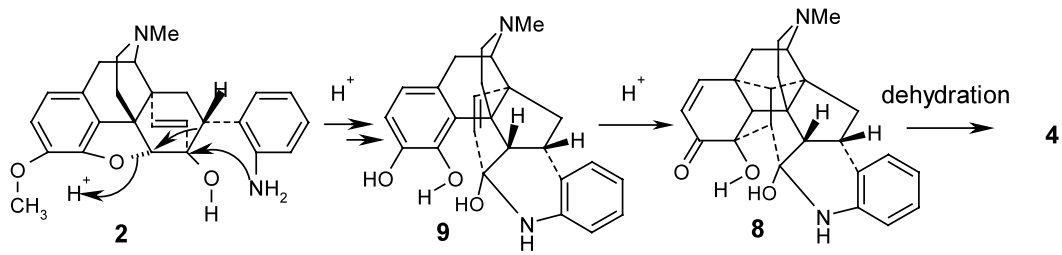


Figure 1. (a) X-Ray crystal structure of compound **4**. (b) 3-Methyl-1,2,3,4,4a,4b,9a,15,15a,15b-decahydro-(4,5);(4a,15)-dimethylenotricyclo(4,3,1,$0^{2,7}$)deca[8,9,1,10-a,b,c]pyrido[4,3-d]-acridin-6-en-9-ol-8-one.



Scheme 2.



Scheme 3.

7. We were interested in isolating this intermediate from the reaction mixture and hoped to confirm that it was the ketone **7**.

As we anticipated, the mass spectrum of this intermediate indicated that it had a molecular weight of 402 (M^+). However, there was only one C=O absorption (1680 cm^{-1}) detected in its IR, and in the ^{13}C NMR (DMSO-d_6) spectrum (192.76, 151.38, 136.9, 132.29, 129.98, 128.46, 127.92, 127.29, 122.86, 97.75, 87.93, 79.18, 66.36, 63.00, 56.05, 54.55, 50.31, 47.14, 44.69, 44.24, 41.36, 34.47, 28.08, 27.39, 23.36), there were only nine sp^2 carbon signals along with 16 sp^3 carbons. Compared to **4**, the C6-imine carbon at 174 ppm had disappeared, while a new quaternary carbon signal showed up at 97 ppm which was absent in **4** (DEPT). All this information suggested that this intermediate was the hydroxyamine (**8**) rather than the ketone **7**. The ^1H NMR spectrum (DMSO-d_6) 11.14 (br, 1 H, C9-OH), 7.62–7.22 (m, 4 H, C11-H, C12-H, C13-H, C14-H), 7.18 (d, 1 H, C6-H, $J_{6,7}=9.8$ Hz), 6.05 (d, 1 H, C7-H, $J_{6,7}=9.8$ Hz), 4.18 (d, 1 H, C9a-H), 4.05–3.95 (t, 1 H, C15a-H), 3.90–3.20 (m, 4 H, C15-H, C2eq-H, C2′-OH, N10-NH), 3.20–2.85 (m, 3 H, C16-H, C4-H, C18β-H), 2.78 (dd, 1 H, C17β-H), 2.60 (s, 3 H, N-CH_3), 2.40–2.00 (m, 4 H, C4b-H, C18a-H, C2ax-H, C1ax-H), 1.85 (d, 1 H, C1eq-H), 1.70 (dd, 1 H, C17α-H, $J_{17\alpha,17\beta}=14.5$ Hz, $J_{17\alpha,15\beta}=7$ Hz) also supported the structure **8**. Incubation of the crystals of **8** for X-ray crystallography analysis was unsuccessful.

At this point, we are not certain whether **8** was formed through **7** or a secondary pathway (Scheme 3), which involves the initial formation of the hydroxyamine **8** followed by annulation of the 6,14-*endo*-ethenylene moiety of intermediate **7** with the A ring aromatic carbons. Since the 7α-aminophenyl nitrogen of **2** is a relatively strong nucleophile, the nucleophilic attack might be concerted with the migration of the carbon cation to form **8**.[6] Final dehydration of **8** would give compound **4**.

Since the imine formation (from **7** to **4**) needs to go through intermediate **8** and in the reaction medium (acidic) most of the amine would be protonated and thus diminish its nucleophilicity, we prefer the former pathway in which formation of the ketone **7** precedes **8**.

In summary, a new rearrangement product, 3-methyl-l,2,3,4,4a,4b,9a,15,15a,15b-decahydro-(4,5);(4a,15)-dimethanotricyclo(4,3,1,$0^{2,7}$)deca[8,9,1,10-a,b,c]pyrido[4,3-a]-acridin-6-en-9-ol-8-one (**4**), has been isolated from the acid-catalyzed *O*-demethylation of 7α-*o*-aminophenyl-6,14-*endo*-ethenotetrahydrothebaine. In addition, the possible mechanism for its formation involving an initial opening of the bridged dihydrofuran of **2** followed by a novel annulation of the 6,14-*endo*-ethenylene moiety of the intermediate **6** with the A ring aromatic carbons is discussed.

Acknowledgements

This work was support by the National Natural Science Foundation of China.

References

1. This report is taken in part from the dissertation submitted by Y. Zeng to the Graduate School of Shanghai Medical University for the M.S. Degree (July, 1995).
2. Qiu, Z.; Zeng, Y.; Yang, J. *Chin. J. Pharm.* **1995**, *26*, 291–292.
3. Bentley, K. W.; Bower, J. D.; Lewis, J. W. *J. Chem. Soc.* (*C*) **1969**, *18*, 2569–2572.
4. Bentley, K. W.; Hardy, D. G. *J. Am. Chem. Soc.* **1967**, *89*, 3281–3292.
5. Bentley, K. W.; Hardy, D. G.; Denis, G.; Meek, B.; Taylor, J. B.; Brown, J. J.; Morton, G. O. *J. Chem. Soc. (C)* **1969**, *17*, 2229–2232.
6. Experimental procedure for 3-methyl-1,2,3,4,4a,4b,9a,15,15a,15b - decahydro - (4,5);(4a,15) - dimethanotricyclo(4,3,1,$0^{2,7}$)deca[8,9,1,10-a,b,c]pyrido[4,3-a]-acridin-6-en-9-ol-8-one (**4**) and 3-methyl-1,2,3,4,4a,4b,9a,9b,10,15,15a,15b-dodecahydro-(4,5);(4a,15)-dimethanotricyclo(4,3,1,$0^{2,7}$)deca[8,9,1,10-a,b,c]pyrido[4,3-a]-acridin-6-en-9,9b-diol-8-one (**8**): A mixture of aminophenylthebaine **1** (5 g, 11.6 mmol) and hydrobromic acid (48%) (60 mL, 316 mmol) was stirred at 120–130°C (oil bath) under an N_2 atmosphere for 20 h. The reaction was cooled to room temperature and the mixture was treated first with aqueous NaOH (40%) and then ammonium hydroxide at ice bath temperature to regulate the pH at 8–9. The resulting suspension was extracted with chloroform (4×200 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was loaded onto a silica gel column (4×20 cm) and was eluted with $CHCl_3$ (1.5 L) followed by 5% methanol in $CHC1_3$ (0.5 L); 10% methanol in $CHC1_3$ (0.5 L) and 15% methanol in $CHCl_3$ (0.5 L). Fractions containing the

desired product were collected. After evaporation of the solvent under reduced pressure, the residue was recrystallized from ethanol to give 0.8 g (18%) **4** as a colorless crystal: mp 242–245°C (dec.) IR cm^{-1}: 3440 (*v* OH), 1660 (*v* C=O), 1630 (*v* N=C); MS 384 (M^+); 700 mg of **4** was converted to its hydrochloride salt by bubbling HCl gas into a solution of **4** in ethanol/ether. mp 306–310°C (dec.); Anal. (C, H, N). $C_{25}H_{24}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$. A similar process and work-up of the reaction after 15 h afforded 150 mg (3%) of **8** as a gummy residue which was converted to its hydrochloride salt by bubbling HCl gas into a solution of **8** in ethanol/ether; mp 316–324°C (dec.); Anal. (C, H, N), $C_{25}H_{26}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$; IR 3400 (br, *v* OH) 1680 (*v* C=O); MS 402 (M^+).