Ring Cleavage of Hydroxyalkyl-Substituted Laudanosines into the Corresponding Isochromans by Chlorothiono- or Chlorothiolformates

Dong-Ung Lee

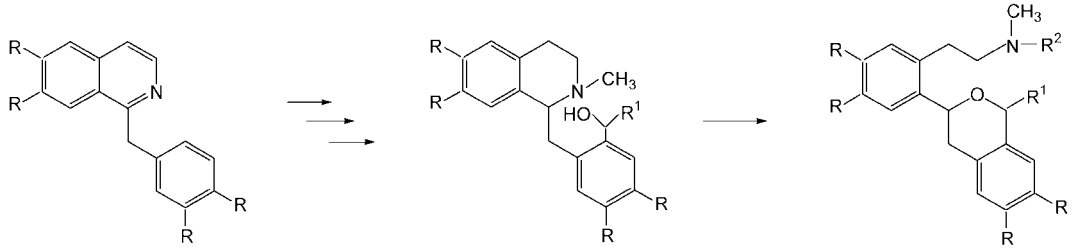
Department of Biochemistry, College of Natural Science, Dongguk University, Gyeongju, Gyeongbuk 780-714, Korea
Received November 27, 2002

Key Words : Ring cleavage, Benzylisoquinolines, Chlorothionoformates

The reaction of tertiary amines with chloroformates leading to dialkylamino formates has first been reported in 1921.[1] After that, ethyl chloroformate was introduced into the chemistry of N-methyl-1,2,3,4-tetrahydroisoquinolines (e.g. **2**, Scheme 1) concerning C-1-N bond cleavage in the ring system by Gadamer.[2] The synthetic value of this reagent, however, is diminished because the CO-OC_2H_5 moiety is fixed very strongly to the N-atom.[2,3] The initial attempt[3] for the preparation of N,N-dimethyl derivatives (e.g. **10**, Scheme 3) failed, but v. Bruchhausen and Knabe[4] have finally overcome this advantage by $LiAlH_4$ reduction. Moreover, ethyl chloroformate degradation of 6'-hydroxymethyllaudanosine (**2**) leads to the 3-phenylisochroman ring system,[5] and the $LiAlH_4$ reduction of the N-methylcarbamate function easily produced the pertinent N,N-dimethylamine derivative **10**. This paper will be devoted to the further discussion on the cleavage of 6'-hydroxymethyl- (**2**) or 6'-hydroxyethyllaudanosine (**3**), a benzylisoquinoline alkaloid, with various chlorothioformates instead of ethyl chloroformate in order to compare the effect of these reagents with that of ethyl chloroformate on the ring cleavage of above isoquinolines.

The starting materials, **2** and **3**, were synthesized from papaverine with trioxane, followed by methyl iodide or ethyl iodide and by sodium borohydride as reported.[6] When **2** was treated with phenyl chlorothionoformate ($ClCSOC_6H_5$), 4-chlorophenyl chlorothionoformate ($ClCSOC_6H_4Cl$), ethyl chlorothiolformate ($ClCOSC_2H_5$), and ethyl chlorodithioformate ($ClCSSC_2H_5$), respectively, the corresponding carbamates **5**-**8** were prepared in relatively low yield (29-42%) in comparison with the high yield (82%)[7] of carbamates obtained by using ethyl chloroformate under the same reaction conditions. The IR spectra of **5** and **6** exhibit -N-C(=S)-O- bands at 1210 cm^{-1} and -C-O-C- bands for 6-ring ether at 1100 cm^{-1}.[5] Contrary to this, -N-C(=O)-S- band in **7** appears intensively at 1660 cm^{-1} (cf. normal carbamate band at 1700 cm^{-1}). The ^1H NMR spectra of all carbamates **5**-**8** include characteristic methine triplets for -CH-O- protons (partially hidden in -OCH_2 signals) at δ 4.8-5.1 ppm, indicating the formation of isochroman ring from **2**.

The yields of these reactions are either similar to or greatly different from each other (29-82%, Scheme 1), depending on the structure of the reagents. For this reason the following possibility may be suggested. The reaction begins with the intermolecular nucleophilic attack of N-atom in laudanosines **2** toward the C=S or C=O carbon in the reagents to furnish the quaternary intermediates (e.g. **2a**, Scheme 2), which forms the isochroman ring by the intramolecular substitution of the hydroxyl group. Because the C=S carbon is less positively charged than the C=O carbon, nitrogen of the isoquinoline moiety can attack the latter carbon more easily, resulting in the high yield (82%) of carbamate **4**. Among the carbamates **5**-**8**, the yield of thiolcarbamate **7** is higher than those of the thionocarbamates **5**, **6**, **8**, and **9**, probably because the partial charge of the thiol carbon of $ClCOSC_2H_5$ is more positive than that of the other reagents.

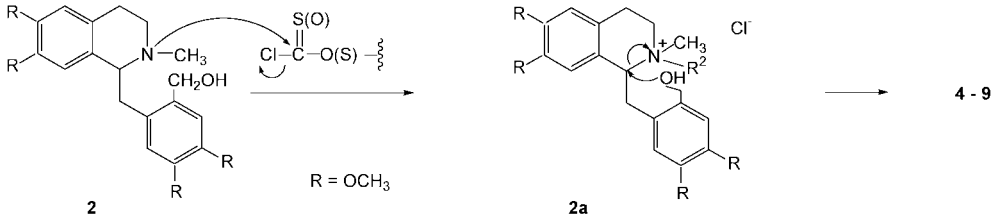


papaverine (**1**)
R = OCH_3

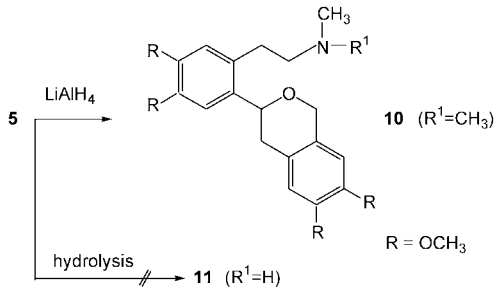
2: R^1 = H
3: R^1 = CH_3

	R^1	R^2	yield
4	H	$COOC_2H_5$	82%
5	H	$CSOC_6H_5$	30%
6	H	$CSOC_6H_4Cl$	31%
7	H	$COSC_2H_5$	42%
8	H	$CSSC_2H_5$	29%
9	CH_3	$CSOC_6H_5$	30%

Scheme 1



Scheme 2



Scheme 3

Analogously to the ring cleavage of **2**, 6'-hydroxyethyllaudanosine (**3**)[5] was also converted with phenyl chlorothionoformate into the corresponding thionocarbamate **9** in low yield (30%).

In addition, when **5** is reduced with $LiAlH_4$, the corresponding N,N-dimethylamine **10** was obtained. N-Monomethylamines (e.g. **11**, Scheme 3) can serve as a more versatile intermediate than N,N-dimethylamines in alkaloid synthesis. The secondary amine **11**, however, could not be directly formed from thionocarbamates **5** under hydrolytic conditions. Although hydrolyses of carbamates with strong acids[8] or bases[9] are commonly known, the isochroman ring in **5** may not be compatible with these hydrolytic conditions (Scheme 3).

Experimental Section

General. Melting points were measured on an Electrothermal IA9100 apparatus and are uncorrected. FT-IR spectra were determined on a Bomem MB 100-10 (nujol). ^{1}H NMR spectra were recorded on a Varian Gemini200 (200 MHz) in $CDCl_3$ with TMS as an internal standard. Column chromatography and TLC were performed using silica gel 60 (Merck, 70-230 mesh) and Kieselgel 60F_{254} (Merck), respectively. All chemicals were bought from Aldrich Co. (USA) except solvents.

6'-Hydroxymethyllaudanosine (2). **2** was prepared as reported by us[6] using papaverine (**1**) as a starting material and trioxane in acetic acid. mp. 99-100 °C (103-104 °C).[7] IR (nujol): 3150 cm^{-1} (OH); ^{1}H NMR: δ 2.17-3.23 (-CH_2- and H-1, m, 7H), 2.30 (N-CH_3, s, 3H), 3.63 (-OCH_3, s, 3H), 3.83 (-OCH_3, s, 6H), 3.88 (-OCH_3, s, 3H), 4.43 (-CH_2OH, s, 2H), 6.27, 6.50, 6.70 and 6.83 (Ar-H, 4 × s, 4H).

3-[2'-(*β*-*N*-Phenyloxythiocarbonyl-*N*-methylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxyisochroman (5). **2** (0.6 g, 1.5 mmol) in 1 : 1 chloroform/ether (7 mL) were treated with 15% KOH (7 mL) and phenyl chlorothionoformate ($ClCSOC_6H_5$, 0.6 mL, 4.5 mmol) under reflux for 2 h. Another 15% KOH (7 mL) and $ClCSOC_6H_5$ (0.3 mL) were added and refluxed for 2 h, then the excess of $ClCSOC_6H_5$ was destroyed by heating with 15% KOH (4 mL). After 1 h, the organic layer was separated and removed to give a crude residue which was purified column chromatography with 8 : 1 : 1 benzene/ether/acetone, furnishing **5** as a pale yellow crystal. Yield 30%. mp. 151 °C. ^{1}H NMR: δ 2.75-3.63 (-CH_2-, m, 6H), 3.25 and 3.34 (N-CH_3, 2 × s, 3H), 3.83 and 3.88 (-OCH_3, 2 × s, 12H), 4.80 (-OCH-, t, J = 5.0 Hz, 1H), 4.97 (-OCH_2-, broad s, 2H), 6.33-7.37 (Ar-H, m, 9H).

3-[2'-(*β*-*N*-Chlorophenyloxythiocarbonyl-*N*-methylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxyisochroman (6). **6** was obtained using 4-chlorophenyl chlorothionoformate ($ClCSOC_6H_4Cl$) by the similar procedure described for **5**. Purification was achieved column chromatography with 8 : 1 : 1 benzene/ether/acetone to give colourless crystals. Yield 31%. mp. 139 °C. ^{1}H NMR: δ 2.75-3.50 (-CH_2-, m, 6H), 3.23 and 3.40 (N-CH_3, 2 × s, 3H), 3.90 and 3.93 (-OCH_3, 2 × s, 12H), 4.77 (-OCH-, t, J = 5.0 Hz, 1H), 4.97 (-OCH_2-, broad s, 2H), 6.37-7.53 (Ar-H, m, 9H).

3-[2'-(*β*-*N*-Ethylthiolcarbonyl-*N*-methylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxyisochroman (7). **7** was prepared as described for **5** using ethyl chlorothiolformate ($ClCOSC_2H_5$). The crude residue was crystallized from hot hexane solution. Yield 42%. mp. 141-142 °C. IR (nujol): 1660 cm^{-1} (CO); ^{1}H NMR: δ 1.23 (-CH_2-CH_3, t, J = 7.0 Hz, 3H), 2.67-3.83 (-CH_2-, m, 6H), 2.90 and 2.93 (N-CH_3, 2 × s, 3H), 3.90 and 3.92 (-OCH_3, 2 × s, 12H), 4.03 (-CH_2-CH_3, q, J = 7.0 Hz, 2H), 4.96 (-OCH-, t, J = 5.0 Hz, 1H), 4.98 (-OCH_2-, s, 2H), 6.60, 6.70, 6.73 and 7.10 (Ar-H, 4 × s, 4H).

3-[2'-(*β*-*N*-Ethyldithiocarbonyl-*N*-methylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxyisochroman (8). **8** was afforded analogously to **5** using ethyl chlorodithioformate ($ClCSSC_2H_5$). The crude residue was purified according to the method for **5**. Yield 29%. mp. 128-130 °C. ^{1}H NMR: δ 1.17 (-CH_2-CH_3, t, J = 7.0 Hz, 3H), 2.47-3.70 (-CH_2-, m, 6H), 2.57 and 2.60 (N-CH_3, 2s, 3H), 3.80 and 3.90 (-OCH_3, 2 × s, 12H), 4.07 (-CH_2-CH_3, q, J = 7.0 Hz, 2H), 5.07 (-OCH-, t, J = 5.0 Hz, 1H), 5.10 (-OCH_2-, s, 2H), 6.28, 6.60, 6.73 and 6.87 (Ar-H, 4 × s, 4H).

3-[2'-(*β*-*N*-Phenyloxythiocarbonyl-*N*-methylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxy-1-methylisochroman (9). **3**[5] (0.8 g, 2 mmol) was treated with phenyl chlorothionoformate under identical conditions for **5** to furnish **9**. Yield 30%. mp. 168-169 °C. ^{1}H NMR: δ 1.67 (-OCH-CH_3, d, J = 7.0 Hz, 3H), 2.73 and 3.67 (-CH_2-, m, 6H), 3.27 and 3.40 (N-

CH_3, 2 × s, 3H), 3.87 and 3.93 (-OCH_3, 2 × s, 12H), 4.67-5.50 (-OCH-, -OCH-CH_3, m, 2H), 6.33-7.50 (Ar-H, m, 9H).

3-[2'-(*β*-*N,N*-Dimethylaminoethyl)-4'5'-dimethoxyphenyl]-6,7-dimethoxyisochroman (10). **5** (0.16 g, 0.3 mmol) in tetrahydrofuran (5 mL) was reduced with $LiAlH_4$ (0.1 g) in refluxing absol. ether (5 mL) for 1 h. Usual work-up using water, subsequent 10% NH_4Cl solution gave the crude residue which was recrystallized with ether to yield **10**. mp. 142-143 °C. ^{1}H NMR: δ 2.33 (-$N(CH_3)_2$, s, 6H), 2.43 and 3.20 (-CH_2-, m, 6H), 3.93 (-OCH_3, s, 12H), 4.95 (-OCH-, t, *J* = 5.0 Hz, 1H), 4.97 (-OCH_2-, s, 2H), 6.60, 6.67, 6.77 and 7.10 (Ar-H, 4 × s, 4H).

Acknowledgement. This work was supported by the Dongguk University Research Grant.

References

1. Bayer, F. German Patent **1911**, *255*, 942 (Chemical Abstract 7: 2096 (**1913**)).
2. Gadamer, J.; Knoch, F. *Arch. Pharm. (Weinheim)* **1921**, *259*, 135.
3. v. Bruchhausen, F.; Schultze, H. *Arch. Pharm. (Weinheim)* **1929**, *267*, 617.
4. v. Bruchhausen, F.; Knabe, J. *Arch. Pharm. (Weinheim)* **1954**, *287*, 601.
5. Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1968**, *301*, 672.
6. Kim, W.-J.; Lee, D.-U.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1984**, *317*, 438.
7. Wiegrebe, W.; Reinhart, H.; Fricke, J. *Pharm. Acta Helv.* **1973**, *48*, 420.
8. Trepanier, D. L.; Sunder, S. *J. Med. Chem.* **1973**, *16*, 342.
9. Abdel-Monem, M. M.; Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 208.