(-)-β-Narcotine: A Facile Synthesis and the Degradation with Ethyl Chloroformate

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(-)-β-Narcotine (**6**), a phthalideisoquinoline alkaloid, was synthesized conveniently by the direct condensation of cotarnine (**1**) and iodomeconine (**2**) prepared by aromatic iodination using thallium trifluoroacetate/KI and by the successive reduction of resulting iodo-β-narcotine (**5**) with aluminum amalgam. Its structure including a stereochemistry was confirmed by instrumental analyses. This synthetic alkaloid was degraded with ethyl chloroformate at room temperature to afford the chloro-carbamate **6b** as a crystalline intermediate, which was unexpectedly converted into the carbinol **8** by exchange of Cl with OH of water contained in the solvents and the ethoxy-carbamate **9**, probably because of ethanol added to chloroform as a solvent stabilizer during the purification by column chromatography.

Key Words : (-)-β-Narcotine, Facile synthesis, Ring cleavage, Ethyl chloroformate

Introduction

Narcotine, a phthalideisoquinoline alkaloid, possesses two chiral centers at C-1 of the tetrahydroisoquinoline nucleus and at C-9 of the γ-lactone ring. Therefore, narcotine should exist in four optically active forms containing enantiomeric and diastereomeric pairs and two racemic mixtures. Among them, (-)-α-narcotine (1R, 9S configuration) is one of the major bases in *Papaver somniferum* L. (Papaveraceae), the sourse plant for opium, while (-)-β-narcotine (1R, 9R configuration) is a synthetic alkaloid. Natural α-narcotine has an antitussive effect and is a weaker analgesic than morphine or codeine which are constituents of opium.

In 1911, Robinson's group has achieved the synthesis of α-narcotine by a direct condensation of cotarnine (**1**) and meconine (**4**).[1] A few years later, this group had firstly synthesized β-narcotine (**6**) with contarnine (**1**) and nitromeconine in five steps, which resulted in poor yields.[2] Although some advanced methods for the preparation of α-narcotine have been developed using modified Bischler-Napieralski cyclization,[3,4] the facile synthesis of β-narcotine has not further been attempted, supposingly because of its no clinical efficacy contrary to α-narcotine. We could conveniently prepare β-narcotine (**6**) by aromatic iodination using cotarnine (**1**) as a starting material.

The bond cleavage between C-1 and N in the narcotine molecule has been accomplished by various methods, *e.g.* Hofmann degradation,[5,6] or using benzyl bromide,[7] *m*-chloroperoxybenzoic acid,[8] cyanogen bromide[9] or chloroformate esters[10,11] to furnish the corresponding enol lactones (stilbenes), keto acids or carbinols. Some of these ring-cleaved products are known to be present in nature as secophthalideisoquinolines.[12] In our previous report,[13] we demonstrated that (-)-β-narcotine (**6**) was degraded by ethyl chloroformate at room temperature to give the carbinol **8** *via* the chloro-carbamate **6b** as a colorless crystalline material, which, however, could not be completely purified. The carbinol **8** was at that time separated by preparative TLC to furnish each diastereomeric pair with an approximate ratio of 5 : 1 (NMR analysis). Recently we have repeated this experiment in order to isolate the intermediate chloro-carbamate **6b** by a pertinent column chromatography and found the formation of unexpected products during separation process. This paper deals with the convenient synthesis of (-)-β-narcotine (**6**) and the structure of unknown degradation product after the treatment of **6** with ethyl chloroformate.

Experimental Section

General. Melting points were measured on an Electrothermal IA9100 apparatus and are uncorrected. Optical rotations were taken on a JASCO DIP-SL polarimeter. UV spectra were recorded on a Shimadzu UV-2001S (MeOH). FT-IR spectra were determined on a Bomem MB 100-10 (nujol). ^{1}H-NMR spectra were obtained on Varian 200 (200 MHz) and Bruker ARX 400 (400 MHz) in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded on a Varian MAT CH5 at 70 eV (EIMS) and Finnigan MAT95 (FDMS). Column chromatography and preparative TLC were performed using silica gel 60 (Merck, 70-230 mesh) and Kieselgel $60F_{254}$ (Merck, 0.5 mm), respectively. All chemicals used were directly obtained commercially unless otherwise noted.

Preparation of cotarnine (**1**). α-Narcotine (4.1 g, 10 mmol) was oxidized with 18% nitric acid (40 g) for 1 h at 50 °C. After standing at room temperature for 30 min, the reaction mixture was filtered to remove opianic acid. The resulting **1** (immonium form) in yellow solution was treated with 40% KOH, affording yellow powders, which were thoroughly washed with water. The crude product was recrystallized with benzene to give compound **1** (pseudo-base form) as pale yellow amorphous crystals. **1** was identified by comparison of NMR and mp. (128-129 °C) with those of the authentic compound.[14] Yield 2.1 g (88.5%). ^{1}H NMR (200 MHz, CD_3OD): δ 2.58 (-NCH_3, s, 3H), 2.70 (-CH_2-, broad s, 2H), 3.31 (-CH_2N-, broad s, 2H), 4.03

(-OCH_3, s, 3H), 4.52 (H-1, broad s, 1H), 5.90 (-OCH_2O-, s, 2H), 6.38 (Ar-H-5, s, 1H).

Preparation of meconine (6,7-dimethoxyphthalide, 4). *o*-Veratric acid (2,3-dimethoxybenzoic acid, 15 g, 0.1 mol) was refluxed with 37% formaldehyde (45 mL) and concentrated HCl (60 mL) for 30 min. After filteration of hot solution, it was cooled to room temperature, then water was added to precipitate crude meconine, which was washed with 10% sodium carbonate and water. Recrystallization with hot water yielded compound **4** as colorless prisms. R_f = 0.63, 4 : 1 $CHCl_3/Et_2O$. Yield 10.2 g (53%). mp. 102-103 °C (101-102 °C)[15]. IR (nujol): 1751 cm^{-1} (lactone); ^1H NMR (200 MHz, $CDCl_3$): δ 3.92 (-OCH_3, s, 3H), 4.10 (-OCH_3, s, 3H), 5.20 (-CH_2-, s, 2H), 7.09 (Ar-H-4, d, J = 8.4 Hz, 1H), 7.25 (Ar-H-5, d, J = 8.4 Hz, 1H).

Preparation of iodomeconine (2). 1) Using $Tl(OCOCF_3)_3$: A mixture of **4** (9.7 g, 0.05 mol) and thallium trifluoroacetate (27.2 g, 0.05 mol) in trifluoroacetic acid (100 mL) was heated for 17 h under reflux. On cooling, the yellow precipitates (aryl thallium ditrifluoroacetate) were stirred with 8.3% KI solution (500 mL) at room temperature for 1 h. After removal of free iodine with sodium metabisulfate (5 g), the filterate was extracted with ether and concentrated to furnish the crude oily material. Crystallization with ether gave **2** as colorless solids, which was colored to deep blue on TLC by spraying of Dragendorff reagent owing to iodide group. R_f = 0.75, 4 : 1 $CHCl_3/Et_2O$. Yield 11.2 g (70%). mp. 123-124 °C (124°C).[1] IR (nujol): 1751 cm^{-1} (lactone); ^1H NMR (200 MHz, $CDCl_3$): δ 3.91 (-OCH_3, s, 3H), 4.10 (-OCH_3, s, 3H), 4.96 (-CH_2-, s, 2H), 7.47 (Ar-H-5, s, 1H).

Using ICl: **4** (0.97 g, 5 mmol) was dissolved in warm glacial acetic acid (4 mL), then gradually mixed with iodine monochloride (1.5 g, 9 mmol), when evolution of HCl gas took place. After 10 min., the reaction mixture was cooled and added with a little water. The excess iodine was removed by a saturated sodium metabisulfate solution and the yellow solution was extracted with ether. Usual work-up of the ether layer led to precipitates, which were recrystallized in methanol, was identified as **2** by direct comparison of mp and TLC with that obtained above. Yield 0.72 g (45%)

Preparation of iodo-β-narcotine (5). **2** (9.6 g, 0.03 mol) was condensed with cotarnine (**1**, 7.2 g, 0.03 mol) in methanol (100 mL) under reflux for 6 h. Water was added to the cooled reaction mixture, affording orange precipitates, which contained **2** and **5**. After standing overnight, the crude solids were filtered, washed with water, and successively purified by column chromatography with 9 : 1 $CHCl_3$/ether to lead compound **5** as fale yellow crystals. Dragendorff reaction: characteristic orange color for alkaloid. R_f = 0.73, 4 : 1 $CHCl_3/Et_2O$. Yield 3.5 g (22%). mp. 179-181 °C (dec.). IR (nujol): 1763 cm^{-1} (lactone); UV (MeOH) λ_{max} (log ε): 317 (3.52), 288 (3.31), 214 (3.52); ^1H NMR (400 MHz, $CDCl_3$): δ 1.93 (-NCH_3, s, 3H), 2.30-2.65 (-CH_2-, m, 2H), 2.70-3.10 (-CH_2N-, m, 2H), 3.91, 4.16, and 4.21 (-OCH_3, 3 × s, 9H), 4.72 (H-1, d, J = 1.7 Hz, 1H), 5.35 (H-9, d, J = 1.7 Hz, 1H), 5.89 (-OCH_2O-, s, 2H), 6.36 (Ar-H-5, s, 1H), 7.47 (Ar-H-3', s, 1H); EIMS: *m/z* (% relative intensity): 319 (2), 220 (100, tetrahydroisoquinoline part), 205 (9), 203 (2), 147 (2), 128 (5), 127 (6).

Preparation of (-)-β-narcotine (6). Fine aluminum foils (1 g, 99.999%, Aldrich) in methanol (10 mL) were refluxed with mercuric chloride (6 g) under nitrogen stream until all aluminum are dissolved. To this aluminum amalgam the solution of **5** (2.2 g, 4 mmol) in anhydrous methylene chloride (10 mL) was added and refluxed for 2 h. After filtration of the hot reaction mixture, the solvent was removed to produce the crude **6** which was purified by column chromatography with 2 : 1 $CHCl_3$/ether, yielding compound **5** as colorless crystals. Dragendorff reaction: characteristic deep orange color for alkaloid. R_f = 0.43, 4 : 1 $CHCl_3/Et_2O$. Yield 1.0 g (60%). mp. 169-171 °C (176 °C).[16] $[\alpha]_D$ -96° (c = 0.2, $CHCl_3$) (-88°)[17]; IR (nujol): 1754 cm^{-1} (lactone); UV (MeOH) λ_{max} (log ε): 310 (3.66), 289 (3.56), 216 (4.66); ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (-NCH_3, s, 3H), 2.42-2.82 (-CH_2-, m, 2H), 3.01-3.17 (-CH_2N-, m, 2H), 3.91, 3.98, and 4.12 (-OCH_3, 3 × s, 9H), 4.21 (H-1, d, J = 2.2 Hz, 1H), 5.53 (H-9, d, J = 2.2 Hz, 1H), 5.84 (-OCH_2O-, s, 2H), 6.36 (Ar-H-5, s, 1H), 6.98 (Ar-H-2', dd, J = 8.3 Hz, 0.8 Hz, 1H), 7.17 (Ar-H-3', d, J = 8.3 Hz, 1H); EIMS: *m/z* (% relative intensity): 220 (100, tetrahydroisoquinoline part), 205 (10), 193 (2); FDMS: m/z 220, 193 (phthalide part).

Preparation of deuterated (-)-β-narcotine (7). **7** was prepared according to the above procedure using CH_3OD instead of CH_3OH. Yield 0.9 g (55%). mp. 181-182 °C (dec.). IR (nujol): 1752 cm^{-1} (lactone); UV (MeOH) λ_{max} (log ε): 310 (3.39), 288 (3.29), 218 (4.32); ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (-NCH_3, s, 3H), 2.40-3.30 (-CH_2-, m, 4H), 3.90, 3.98, and 4.12 (-OCH_3, 3 × s, 9H), 4.20 (H-1, d, J = 2.2 Hz, 1H), 5.51 (H-9, d, J = 2.2 Hz, 1H), 5.86 (-OCH_2O-, s, 2H), 6.35 (Ar-H-5, s, 1H), 7.16 (Ar-H-3', s, 1H); EIMS: *m/z* (% relative intensity): 220 (100, tetrahydroisoquinoline part), 204 (10), 202 (3), 194 (2), 147 (2); FDMS: *m/z* 220, 194 (phthalide part).

Degradation of β-narcotine (6) with ethyl chloroformate. **6** (4.13 g, 0.01 mol) was dissolved in methylene chloride (10 mL) and stirred with ethyl chloroformate (4 mL, 0.04 mol) at room temperature for 5 h. The solvent and the excess reagent were thoroughly removed to afford the crude product, which was immediately subjected to column chromatography with 4 : 1 $CHCl_3$/ether for isolation of the intermediate chloro-carbamate (**6b**). Chromatographic separation resulted in one solid product which was identified as carbinol **8** by comparison of its spectral data with those of authentic sample[18] and one unknown oily material. This oil was further purified by preparative TLC (4 : 1 $CHCl_3/Et_2O$), yielding a pure oily compound (R_f = 0.43, 4 : 1 $CHCl_3$/ Et_2O), of which structure was determined to be ethoxy-carbamate (**9**) by the following spectral data. IR (neat): 1767 (lactone), 1696 cm^{-1} (carbamate); UV ($CHCl_3$) λ_{max}: 308, 304 (shoulder), 241; ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 and 1.24 (2 × -OCH_2CH_3, 2 × t, J = 7.0 Hz, 2 × 3H), 2.71-2.95 (-CH_2-, m, 2H), 2.82 (-NCH_3, s, 3H), 3.47-3.70 (-CH_2N-, m, 2H), 3.83 (-OCH_3, s, 3H), 3.95-4.25 (2 × -OCH_2CH_3, 2 × t, hidden in OCH_3 protons, 2 × 2H), 4.08 (2 × -OCH_3, s, 6H),

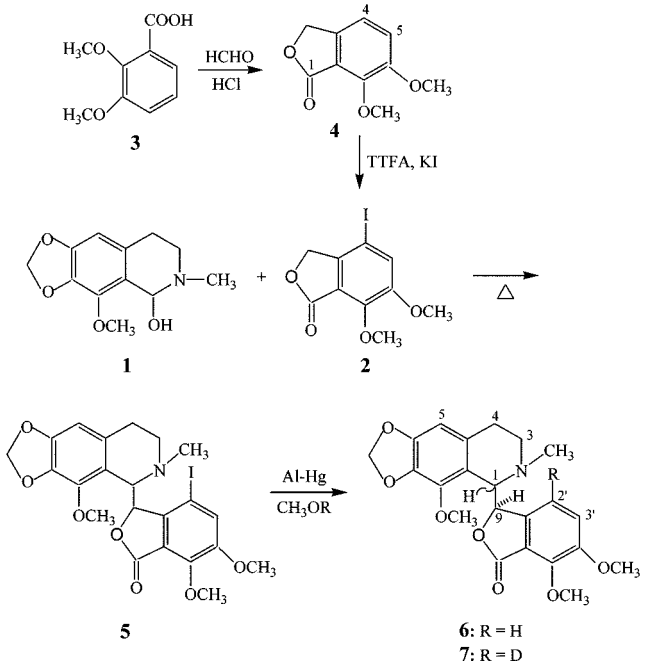
4.70 (H-1, d, J = 2.2 Hz, 1H), 5.97 (H-9, d, hidden in -OCH_2O-, 1H), 5.98 and 6.93 (Ar-H-2' and 3', AB, J = 8.3 Hz, 2H), 5.99 (-OCH_2O-, s, 2H), 6.47 (Ar-H-5, broad s, 1H); EIMS: m/z (% relative intensity): 338 (48), 292 (100), 264 (31), 218 (64), 193 (40), 149 (25); PI-DCIMS (NH_3): *m/z* 549 [$(M+NH_4^+)^+$], 532 (MH^+), 503 [(**9a**+NH_4^+)$^+$], 486 (MH^+-EtOH, protonated **9a**).

Results and Discussion

Robinson and Hope have reported that cotarnine is condensed with nitromeconine to give nitro-β-narcotine, which is converted over three steps into β-narcotine as illustrated below.[2] Total yield seems to be very low.

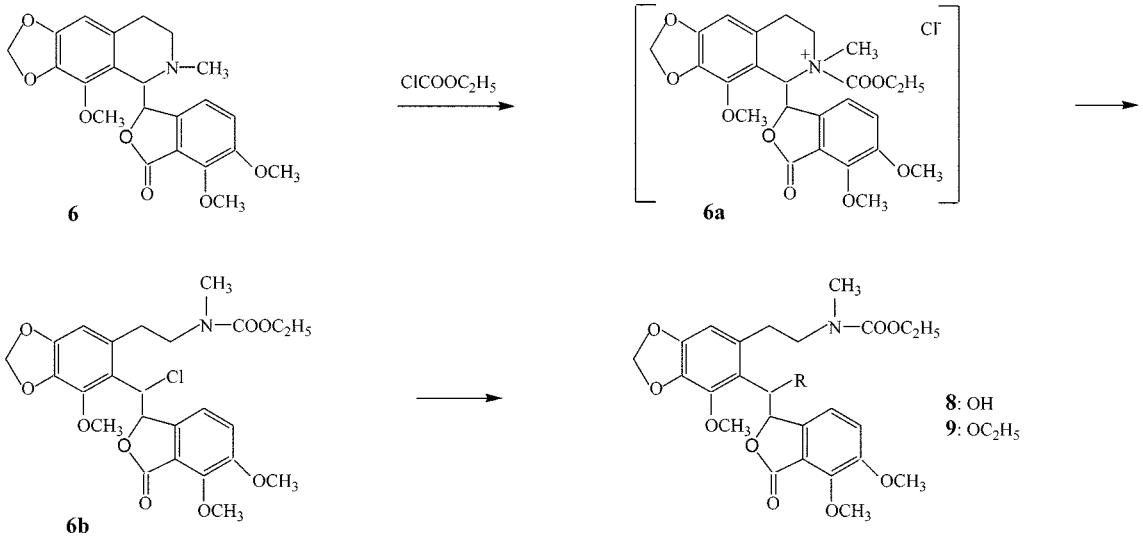
Cotarnine (**1**) + nitromeconine
⟶ nitro-β-narcotine
⟶ amino-β-narcotine
⟶ hydrazino-β-narcotine ⟶ β-narcotine (**6**)
⟶ iodo-β-narcotine ⟶

As already stated, narcotine is consisting of two individual moieties - the tetrahydroisoquinoline ring and the phthalide group, and the bond combining these two parts is relatively weak. The electron impact (EI) mass spectrum of narcotine shows no molecular ion which is not detected even by field desorption (FD) mass spectrometry (see Exp. Section). This may be the most important reason for diminishing the yield of synthetic narcotine. Therefore, to improve the yield of β-narcotine the reaction step should be shortened. We could reduce two synthetic steps by direct condensation of cotarnine (**1**) and iodomeconine (**2**) (Scheme 1). *o*-Veratric acid (2,3-dimethoxybenzoic acid, **3**) was converted to meconine (6,7-dimethoxyphthalide, **4**) using HCHO and HCl *via* 3,4-dimethoxy-2-carboxybenzyl alcohol as an intermediate by a known method.[15] **4** was iodinated by electrophilic aromatic



Scheme 1. Synthetic procedure of (-)-β-narcotine (**6**).

thallation using thallium trifluoroacetate, successively with KI to furnish iodomeconine (**2**, 70% yield) which also could be prepared by iodine monochloride with a poor yield (45%). Compound **2** was condensed with cotarnine (**1**)[14] to form iodo-β-narcotine (**5**). The stereochemistry of **5** was determined by ^{1}H NMR spectroscopy: α- and β-narcotine have easily been distinguished from each other by comparison of the chemical shifts of the signal H-3' and the coupling constant of signals between H-1 and H-9.[19] ^{1}H NMR spectrum of **5** exhibits that the signal H-3' is shifted to δ 7.47 ppm in contrast to the chemical shift δ 7.17 ppm in authentic β-narcotine[18] which lacks electronegative substituent at C-2'. The proton H-3' in α-narcotine is appeared at 6.96 ppm as doublet. Moreover, the coupling constants of signals H-1 and



Scheme 2. Degradation of (-)-β-narcotine (**6**) with ethyl chloroformate at room temperature.

H-9 in iodo-*β*-narcotine (**5**) were calculated to be J = 1.7 Hz which corresponds with J = 2.2 Hz in *β*-narcotine. These values are apparantly different from the coupling constant (J = 4.2 Hz) of the same protons in *α*-narcotine. Above NMR data indicate that **5** is an *β*-isomer. Compound **5** could not be prepared by direct aromatic iodination of narcotine using thallium trifluoroacetate or iodine monochloride, because the bond fission between H-1 and H-9 occurred initially under acidic conditions. Finally, **5** was reduced with aluminum amalgam in methanolic solution to afford *β*-narcotine (**6**) whose structure was confirmed by comparison of the ^{1}H NMR spectrum of authentic *β*-narcotine. When **5** is treated with aluminum amalgam in CH_3OD solution instead of CH_3OH, deuterated *β*-narcotine (**7**) was produced. Therefore, these whole synthetic procedures may also be applied for the preparation of some *β*-narcotine derivatives substituted at C-2' position.

The C-N bond fission of the piperidine ring in phthalide-isoquinolines has firstly been achieved by Hofmann using methyl iodide and a strong base. (Hofmann degradation)[5] After that, Gadamer has introduced ethyl chloroformate (ECF) as a reagent for the cleavage of C-N bond in the alkaloid chemistry.[20] We have previously discussed that *α*- and *β*-narcotine (**6**) yielded the corresponding diastereomeric carbinols by treatment with ECF at room temperature in ratios of approximately 13 : 1 and 5 : 1 (^{1}H NMR), respectively with a high stereoselectivity.[13] Recently this experiment was repeated to isolate the chloro-carbamate **6b** (Gadamer's intermediate, Scheme 2). As we already reported,[21] the degradation of benzylisoquinolines with ECF led primarily to the hypothetical quaternary carbamate such as **6a** and the following chloro-carbamate such as **6b** which is an optically active intermediate with a relative stability. In the present study, we tried to isolate this kind of intermediate **6b** obtained from *β*-narcotine (**6**) with ECF by pertinent column chromatography with the solvent system 4 : 1 $CHCl_3/Et_2O$.

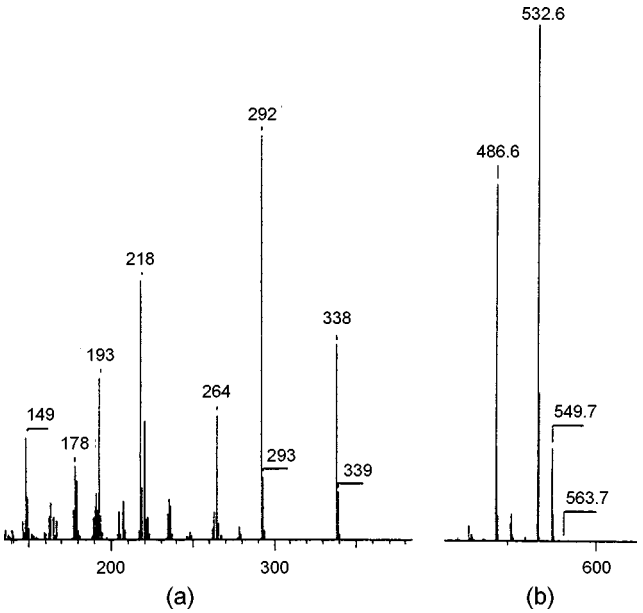
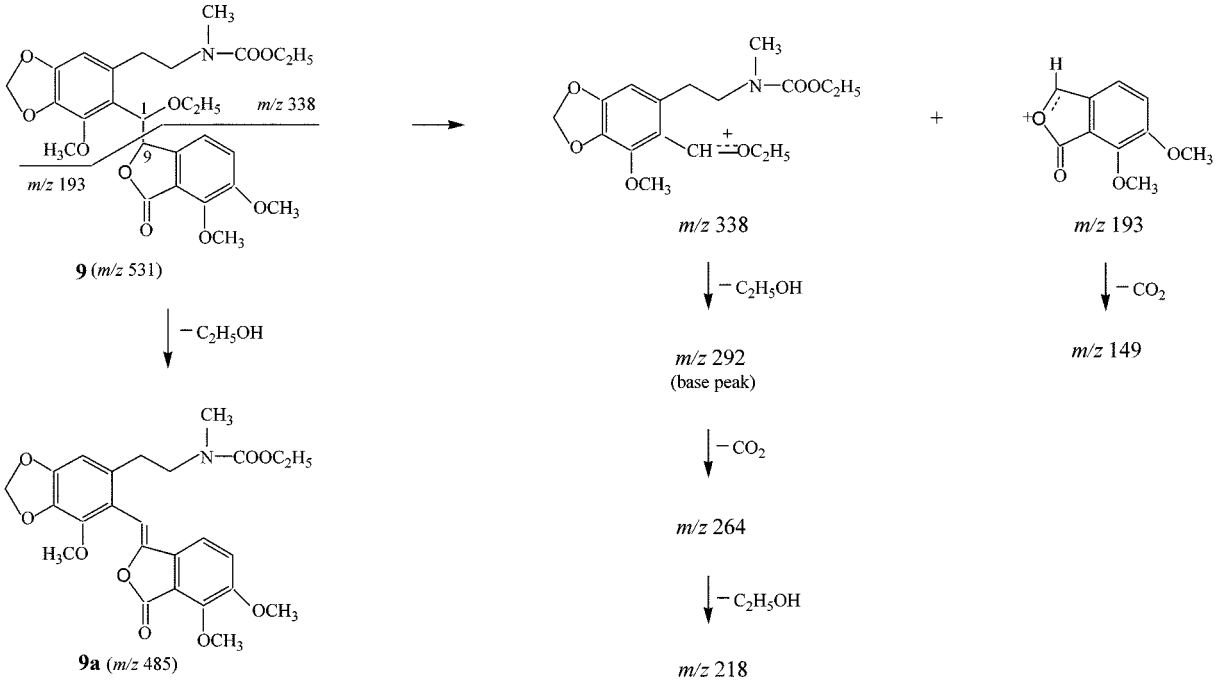


Figure 1. (a) Electron impact mass spectrum (EIMS) of the ethoxy-carbamate **9** at 70 eV. (b) Positive ion-direct chemical ionization mass spectrum (PI-DCIMS) using NH_3. The fragment ions at *m/z* 532 and *m/z* 486 correspond to the protonated molecular ions of **9** and **9a**, respectively.

However, crude **6b** could not be purified by column chromatography, rather was converted to the carbinol **8** and the ethoxy-carbamate **9**. Carbinol **8** was previously obtained by refluxing of the crude chloro-carbamate **6b** with water,



Scheme 3. Fragmentation pathway of the ethoxy-carbamate **9** after electron impact at 70 eV.

but **9** has not yet been synthesized or isolated from natural sources. The structure of compound **9** was assigned by spectral data. Its ^{1}H NMR spectrum exhibited two ethyl signals existing in carbamate moiety and ethoxy group at C-1. Further evidence was established by EIMS (Figure 1a): the bond between C-1-C-9 was initially cleaved in the gas phase to produce fragment ions at *m/z* 193 (40% intensity) and *m/z* 338 (48% intensity). The latter ion loses one C_2H_5OH molecule to form the ion at *m/z* 292 as a base peak, successive elimination of CO_2 and another C_2H_5OH molecule yields the ion at *m/z* 218 (64% intensity) (Scheme 3). This structure was finally confirmed by positive ion-direct chemical ionization mass spectrometry (PI-DCIMS, NH_3) (Figure 1b), presenting the fragment ions at *m/z* 532 for MH^+ and *m/z* 549 for $[(M+NH_4)^+]^+$.

The EIMS spectrum of **9** exhibited interestingly one more molecular ion at *m/z* 486 as MH^+ whose structure might be stilbene **9a** originated from the loss of C_2H_5OH in the molecule of **9** (Scheme 3).

The carbinol **8** must be appeared in the column by exchange of Cl in the chloro-carbamate **6b** with OH of water contained in the solvents and the compound **9** is produced during the purification probably because of ethanol added to chloroform as a solvent stabilizer.

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