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Stereochemistry of the Degradation Product of (-)-α -Narcotine and Its Analogs with Ethyl Chloroformate

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A (-)-α-narcotine from *Papaver sommiferum* was refluxed with ethyl chloroformate to give the diastereomeric chloro-carbamate mixture and the Z/E-enol lactones as Z:E=1:1.1 ratio in HPLC analysis. After photoisomerization with UV (254 nm), the Z/E ratio was drastically changed to Z:E=7:1, which may indicate that the E-isomer was easily converted to the Z-isomer due to photoisomerization. The photoisomerization of the Z/E-enol lactones and the different stereochemistry of the degradation product of β-narcotine, deuterated β-narcotine and β-hydrastine with ethyl chloroformate will also be discussed.

Key words – α-Narcotine, β-Narcotine, β-Hydrastine, Z/E-Enol lactone, Stereochemistry

Narcotine, a phthalideisoquinoline alkaloid, is one of the major bases in *Papaver somniferum* L. (Papaveraceae) which is the source plant for opium. This molecule 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 stereoisomers containing enantiomeric and diastereomeric pairs. Among them, natural (-)-α-narcotine (**1**) has an antitussive effect and is a weaker analgesic than morphine or codeine which are constituents of opium.

The bond cleavage between C-1 and N in the narcotine molecule has been accomplished by various methods, e.g. Hofmann degradation[3], or using benzyl bromide[7], *m*-chloroperoxybenzoic acid[5], cyanogen bromide[6] or chloroformate esters[8,10] to furnish the corresponding Z/E-enol lactones (stilbenes), keto acids or carbinols. Some of these ring-cleaved products are known to be present in nature as secophthalideisoquinolines[4].

However, the stereochemistry of the degradation products of α-narcotine and the related phthalideisoquinolines has not fully investigated and is still interesting field in the alkaloid chemistry. In the present report, we discuss the stereochemistry of the Z/E-enol lactones obtained from α-narcotine and its anlogs, β-narcotine, deuterated β-narcotine and β-hydrastine refluxed with ethyl chloroformate. We also described the stereoselective formation and unusual photoisomerization of the Z/E-isomers.

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Materials and Methods

General

α-Narcotine, β-hydrastine and ethyl chloroformate were purchased from Sigma Chemical Co. (St. Louis, MO. USA). β-Narcotine and deuterated β-narcotine were prepared by our previous method[1]. HPLC analysis was carried out with a Spectra-Physics 8700 (Irvine, CA, USA) equipped with a Spherisorb Si column (250×4 mm, 5 μm) (flow rate: 2.0 ml/min, pressure : 1260 psi, UV : 254 nm).

Degradation of α -narcotine (1) with ethyl chloroformate

(-)-α-Narcotine (**1**, 0.2 g, 0.5 mmol) in dichloromethane (2 ml) was refluxed with fresh ethyl chloroformate (ECF, 0.2 ml, 2 mmol) for 4h. After complete removal of the solvent and excess ECF, the mixture was analyzed with HPLC using 25% tetrahydrofuran in *n*-hexane as an eluent. Retention time (min): **2**, 9.22; **3**, 8.21; **4**, 10.70; **5**, 5.48. Each compound was identified by the comparison with authentic compounds[10] to be the corresponding enol lactones (**2**, **3**), chloro-carbamates (**4**, **5**) and a very small amount of *N*-desmethyl-*N*-carbethoxynarcotine[11] (Rt=6.99 min).

Separation of enol-lactone isomer mixture

Above crude reaction mixture was subjected to column chromatography using silica gel with chloroform-ether 4:1 as an eluent to yield the Z/E-isomer mixture. The isomer ratio of the mixture was determined by HPLC under the above conditions. This isomer mixture was further separated by column chromatography (chloroform-ether 6:4) to furnish

Z- (pale yellow crystal) and E-enol lactone (pale yellow oil) individually.

Photoisomerization of Z/E-enol lactone mixture

The solution of Z- and E-enol lactones in chloroform was irradiated in pyrex bottle with UV (254 nm) for 30 min. and 330 min., then respectively determined by HPLC under the above conditions.

Degradation of β-narcotine (6), β-hydrastine (7) and deuterated β-narcotine (8) with ethyl chloroformate

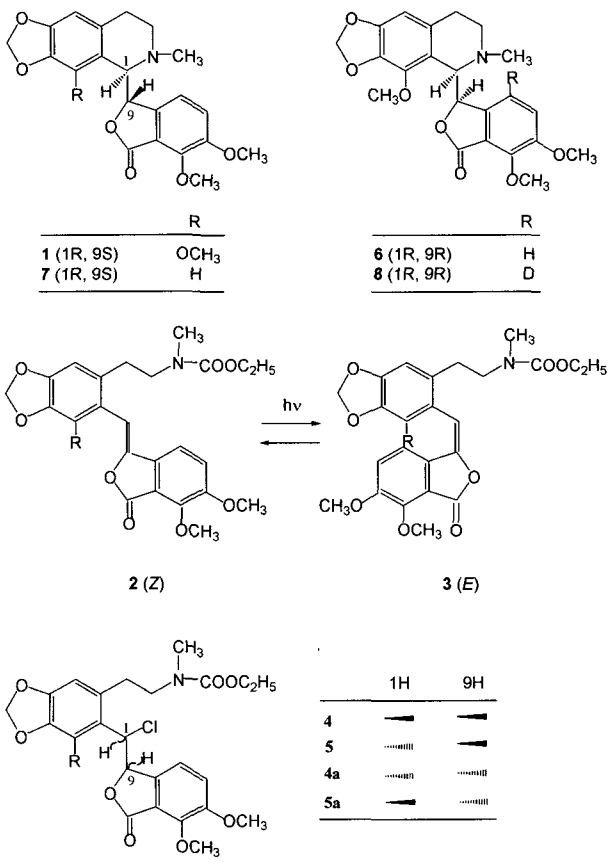
β-Narcotine (**6**) and deuterated β-narcotine (**8**) were prepared by our authentic method[1]. Treatment of **6**, **7** and **8** with ECF were performed as described above to give the corresponding Z/E-enol lactones and/or the chloro-carbamates, which were respectively analyzed by HPLC under the above conditions.

Results and Discussion

In our previous reports[10,11], the stereochemistry of the Z- and E-enol lactones as well as the diastereomeric chloro-carbamates and carbinols derived from α-narcotine (**1**) with ethyl chloroformate (ECF) has been discussed. Recently we also investigated the degradation of β-narcotine (**2**) with ECF at room temperature, yielding the corresponding carbinols and the unexpected ethoxy derivative[9].

α-Narcotine was treated with ECF under reflux to afford Z- and E-enol lactones (**2** and **3**) and the diastereomeric chloro-carbamates (**4** and **5**) (Scheme 1). The Z/E-isomers were produced with a high stereoselectivity, the yields of both isomers were about 70% and 10%[11], respectively, after the chromatographic separation. Such a different stereoselectivity in the similar *cis/trans-* or Z/E-isomers has also been found in pertinent stilbenes[1,2] and secophthalideisoquinolines[1,2]. Shamma et al.[12], however, could not obtain any Z/E-enol lactone by mild Hofmann degradation (basic conditions) of α-narcotine.

We recently repeated the reaction of α-narcotine (**1**) with ECF in refluxing dichloromethane by our previous method [11]. The crude reaction mixture was directly detected by HPLC to give five peaks for the Z- (**2**) and E-enol lactones (**3**), the chloro-carbamates (**4** and **5**), and the very small peak (Rt=6.99 min) identified as N-desmethyl-N- carbethoxynarcotine (Fig. 1). Among the enol lactones, the thermodynamically less stable E-isomer (**3**) was unexpectedly produced a little more than Z-isomer (**2**) with ratio of 1.12:1. However, as mentioned above, when the reaction mixture was separated by column chromatography, the yield of Z-isomer was ca. 7-fold higher than that of E-isomer. The isolated oily E-isomer from the column crystallized even upon grinding with glass rod without any contact with solvent, being converted into crystalline Z-isomer. E-isomer was also easily photoisomerized to Z-isomer by sunlight. These observations may explain why Z-isomer was much more formed than E-isomer after chromatographic separation of the isomer mixture.



Scheme 1.

In contrast to the case of α-narcotine, β-narcotine (**2**) afforded two chloro-carbamates (**4a** and **5a**) and practically no Z/E-enol lactones in the HPLC chromatogram (Fig. 1). This striking difference between α- and β-isomers may be originated from the different stereochemistry at C-9 (9S for α- and 9R for β-narcotine).

We additionally investigated the formation of the Z/E-enol lactones from the similar compounds, deuterated β-narcotine (**8**), and β-hydrastine (**7**), with ECF in order to find the effect of the substituent in the molecule (Table 1).

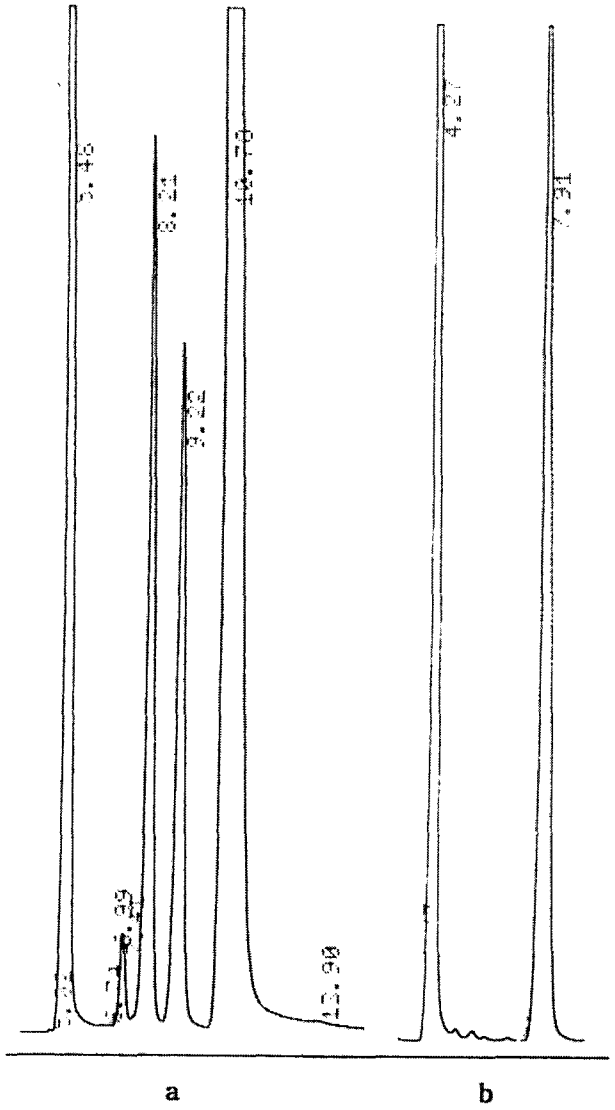


Fig. 1. HPLC chromatograms of the reaction mixtures of α -narcotine (a) and β-narcotine (b) with ethyl chloroformate under reflux. Two peaks in b correspond to the chloro-carbamates. Retention time (min): **2** (9.22), **3** (8.21), **4** (10.70), **5** (5.48), *N*-desmethyl-*N*-carbethoxynarcotine (6.99).

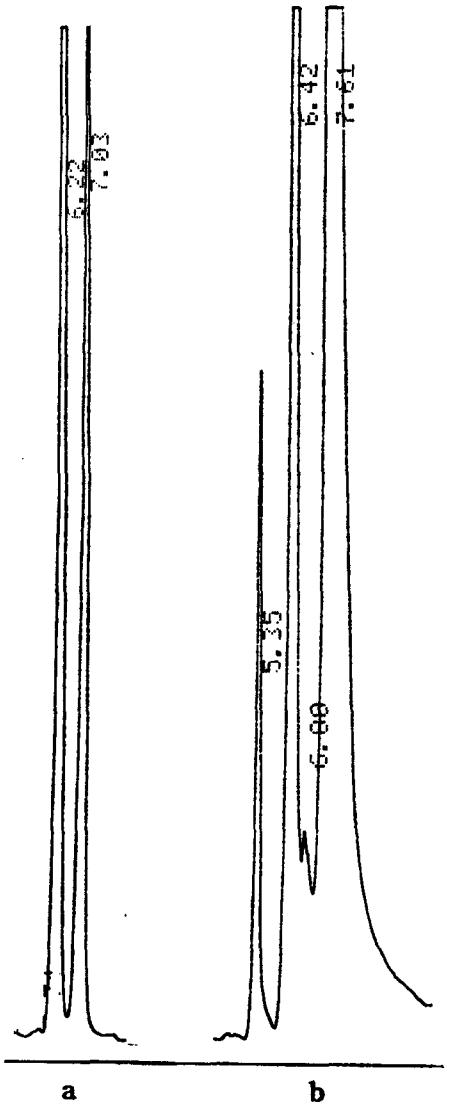


Fig. 2. HPLC chromatograms of the reaction mixtures of deuterated β-narcotine (a) and β-hydrastine with ethyl chloroformate under reflux. Retention time (min): *Z*-(7.03 or 7.61) and *E*-enol lactone (6.22 or 6.42). The peak at 5.35 min in b correspond to the chloro-carbamate.

The HPLC chromatogram (Fig. 2a) of the *Z*/*E*-enol isomer mixture resulted from **8** shows very different pattern from the degradation of α-narcotine: both isomers were main products showing the isomer ratio of 1:1.44, and the corresponding chloro-carbamates were practically not produced. Such a drastic effect of deuterium instead of hydrogen on the different formation of the stereoisomers could not be explained up to now. This needs further studies. In case of

Table 1. Comparison of reaction products from narcotine and its analogs with ethyl chloroformate under reflux

compound	config.	major product	minor product	Z/E ratio
α-narcotine (**1**)	1R, 9S	carbamates (4, 5)	Z < E	1 : 1.12
β-narcotine (**6**)	1R, 9R	carbamates (4a, 5a)	-	
β-hydrastine (**7**)	1R, 9S	Z > E	carbamates (4, 5)	ca. 5 : 1
D-β-narcotine (**8**)	1R, 9R	Z < E	-	1 : 1.44

β-hydrastine (**7**) which lacks a methoxy group at C-8 in α-narcotine (**1**) and contains a same (1R, 9R)-configuration with **1**, the yield of *Z*-isomer was about 5 times more than that of the *E*-isomer (Fig. 2b), which probably points toward the steric hinderence. Shamma and his coworkers[3] could separate the *Z*/*E*-enol lactones from the Hofmann degradation of β-hydrastine to give 77% and 6%, respectively. Considering our findings with HPLC analysis, their results may suggest that more *E*-isomer in the reaction mixture was converted into the *Z*-isomer during the separation procedure.

The *cis-trans* equilibrium of olefins has been accomplished by various isomerization catalysts[12], however, these methods were applicated for olefins having no steric hinderence. Moreover, the thermodynamic equilibrium of the sterically hindered molecules such as **2** and **3** by irradiation has little been studied in the field of alkaloid chemistry.

We tried to transform the more stable *Z*-isomer to the less stable *E*-isomer by irradiation with UV (254nm). After the reaction without irradiation, the isomer mixture obtained by column chromatography was analyzed using an efficient HPLC method to exhibit the isomer ratio of 78.1 (*Z*):21.9 (*E*) (Fig. 3a). After irradiation for 30min. and 330min., the *Z*-isomer decreased to 65% (Fig. 3b) and 56% (Fig. 3c), respectively. This experiment apparantly shows that the stable *Z*-isomer can be isomerized into the less stable *E*-isomer by irradiation in spite of the steric hinderence in the *E*-isomer.

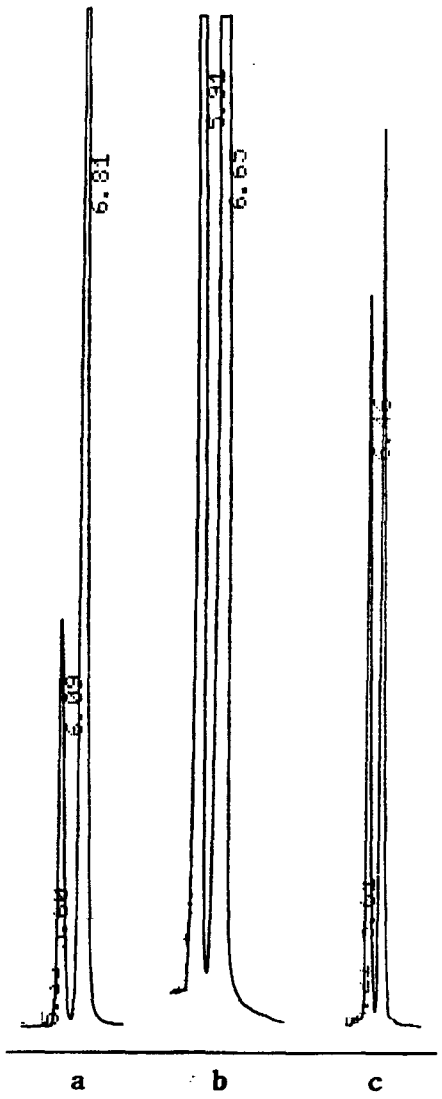


Fig. 3. HPLC chromatograms after photoisomerization of the *Z*/*E*-isomer mixture. Irradiation times: 0 min (a), 30 min (b), and 330 min (c). Retention time (min) of *Z*-enol lactone: 6.81 (a), 6.65 (b) and 6.46 (c).

Acknowledgement

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References

1. Batteraby, A. R. and I. A. Greenock. 1961. Cis- and trans-3,3',4,4'-tetramethoxystilbenes. *J. Chem. Soc.* 2592-2593.
2. Battersby, A. R. and B. J. Haper. 1962. Alkaloid biosynthesis. Part I. The biosynthesis of papaverine. *J. Chem. Soc.* 3526-3533.
3. Blasko, G., V. Elango, B. Sener, A. J. Freyer and M. Shamma. 1982. Secophthalideisoquinolines. *J. Org. Chem.* **47**, 880-885.
4. Blasko, G., D. J. Gula and M. Shamma. 1982. The phthalideisoquinoline alkaloids. *J. Nat. Prod.* **45**, 105-122.
5. Iwasa, K., M. Kamigauchi, M. Sugiura and N. Takao. 1987. Conformations of phthalideisoquinoline salts and N-oxides. *J. Nat. Prod.* **50**, 1083-1088.
6. Kerekes, P. and G. Gaal. 1980. Reactions of narcotine isomers with cynogen bromide. *Acta Chim. Acad. Sci. Hung.* **103**, 343-353.
7. Klötzer, W., S. Teitel and A. Brossi. 1972. Eine neue Synthese von Nornarcein. *Monatsh. Chem.* **103**, 1210-1212.
8. Klötzer, W., S. Teitel and A. Brossi. 1972. Die Totalsynthese des Alkaloids Rhoeadin. *Helv. Chim. Acta* **55**, 2228-2232.
9. Lee, Dong-Ung. 2002. (-)-β-Narcotine: A facile synthesis and the degradation with ethyl chloroformate. *Bull. Kor. Chem. Soc.* **23**, 1548-1552.
10. Lee, Dong-Ung, E. Eibler, K. K. Mayer and W. Wiegrebe. 1995. Stereochemical elucidation of the reaction products of α-narcotine with ethyl chloroformate. *Chem. Pharm. Bull.*

43, 1995-1997.
11. Lee, Dong-Ung, K. Iwasa, M. Kamigauchi, N. Takao and W. Wiegrebe. 1991. Degradation of some phthalideisoquinolines with ethyl chloroformate-stereochemical aspects. *Chem. Pharm. Bull.* **39**, 1944-1948.
12. Moussebois, C. and J. Dale. 1966. A method of cis, trans isomerization of nonconjugated olefins without double-bond migration. *J. Chem. Soc.* 260-264.

초록 : (-)-α -Narcotine과 유사화합물을 ethyl chloroformate로 반응시 생성된 분해물의 입체화학

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양귀비의 성분중 하나인 (-)-α-narcotine은 ethyl chloroformate와 가온반응시 diastereomeric chloro-carbamate 혼합물과 Z/E-enol lactone 혼합물을 생성하였는데 이 중에서 Z/E-isomer의 생성비를 HPLC로 측정한 결과 Z:E= 1:1.12로 나타나 열역학적으로 불안정한 E-isomer가 다소 많이 생성되었다. 그러나 이 isomer 혼합물을 chromatography로 각각 분리한 결과, 그 생성비는 Z:E=7:1로 나타나 분리도중에 column 내에서 E-isomer가 보다 안정한 Z-isomer로 대부분 변하였음을 알 수 있었다. Z/E-isomer의 생성비가 유사한 구조의 화합물에서 어떻게 변하는지를 관찰하기 위하여 β-narcotine, deuterated β-narcotine 및 β-hydrastine을 대상으로 동일한 조건하에 반응시킨 결과, 이들의 isomer 생성비율이 구조에 따라 크게 차이가 있음을 알 수 있었으며 그 이유를 설명하였다. 한편, 일반적인 보고와는 달리, narcotine에서 생성된 안정한 Z-isomer는 광화학반응에 의해 불안정한 E-isomer로 쉽게 변한다는 사실도 확인하였다.