Stereochemical Elucidation of the Reaction Products of α-Narcotine with Ethyl Chloroformate

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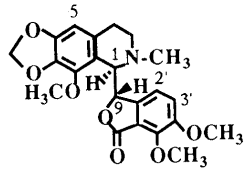
α-Narcotine (1) was treated with ethyl chloroformate by refluxing in dichloromethane to afford six products, which were separated by preparative high-performance liquid chromatography (HPLC). Their stereochemistry and structures were elucidated. This reaction proceeded initially to the chloro-carbamates and successively to the corresponding carbinols. In addition, *N*-desmethyl-*N*-carbethoxynarcotine (3), found in the HPLC chromatogram, was identified by direct comparison with synthetic 3; this compound had caused difficulty in our previous mass spectrometric investigations.

Key words α-narcotine; ethyl chloroformate; high-performance liquid chromatography; absolute configuration; *E*/*Z*-enol lactone; chloro-carbamate

In a previous study[1] on the reaction of some phthalideisoquinolines with ethyl chloroformate (ECF), we reported that treatment of α- and β-narcotine as well as α- and β-hydrastine with ECF furnishes the corresponding diastereomeric carbinols at room temperature and *E*/*Z*-enol lactones under reflux. We assumed that the chloro-carbamate (or a mixture of pertinent diastereomers), which could be isolated in a crude state only,[1] was the precusor of the carbinols. Here we describe the separation of these intermediates—compounds **2** and **6** (Chart 1)—by an efficient HPLC method which became available for us in the meantime, the elucidation of their stereochemistry and their straightforward hydrolysis to the diastereomeric carbinols. We have also reported on the abnormal fragmentations of the above *E*- and *Z*-isomers in the gas phase upon electron impact.[2] We also show here that this apparent abnormality was due to a trace of compound **3** (see below), which could be detected by HPLC.

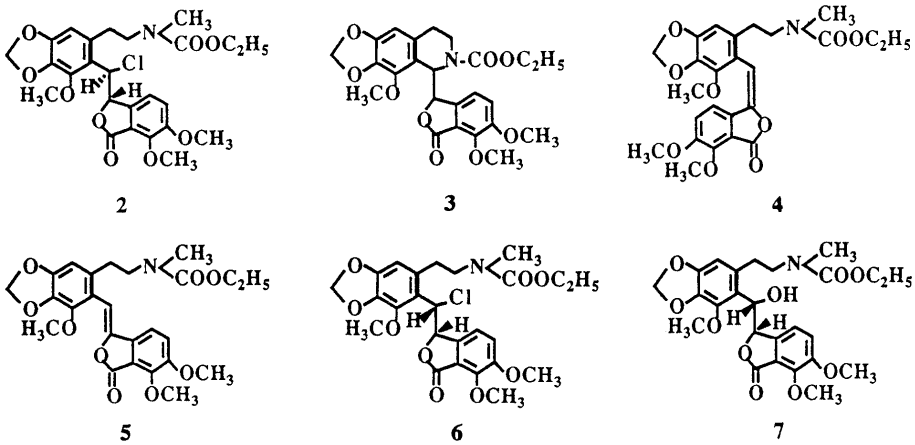
(−)-α-Narcotine (**1**, Chart 2) was refluxed in dichloromethane with excess ECF.[1] Then the mixture was thoroughly evaporated and directly analyzed by HPLC to give six peaks of compounds **2**—**7** (Fig. 1), which were isolated preparatively by HPLC. The very small peak of the carbinol **7** could be identified using analytical HPLC by comparison with authentic **7** prepared from **6** with water.

The electron impact mass spectra (EI-MS) of the chlorides **2** and **6** are identical, suggesting that **2** and **6** are diastereomers. The chemical shifts of the signals of 9-H, 2′-H, and 3′-H in both chlorides are significantly different (see Experimental). From these ^{1}H-NMR spectra, the absolute configuration of the chloro-carbamate **6** could be determined as 1*S*,9*S* by direct comparison of the chemical shifts and coupling constants with the corresponding signals of the carbinol **7**, which has 1*S*,9*S* configuration.[1] The chloride **2** was converted to the carbinol **8** (Chart 3) with water under reflux. Carbinols **8** and **7** are diastereomers. Since the absolute configuration of the carbinol **7** has been established to be 1*S*,9*S*,[1] the absolute configuration of **8** must be 1*R*,9*S*. Because the



(1R,9S)-**1**

Chart 2



2 **3** **4**

5 **6** **7**

Chart 1. Degradation Products Obtained from α-Narcotine (**1**) with Excess ECF under Reflux

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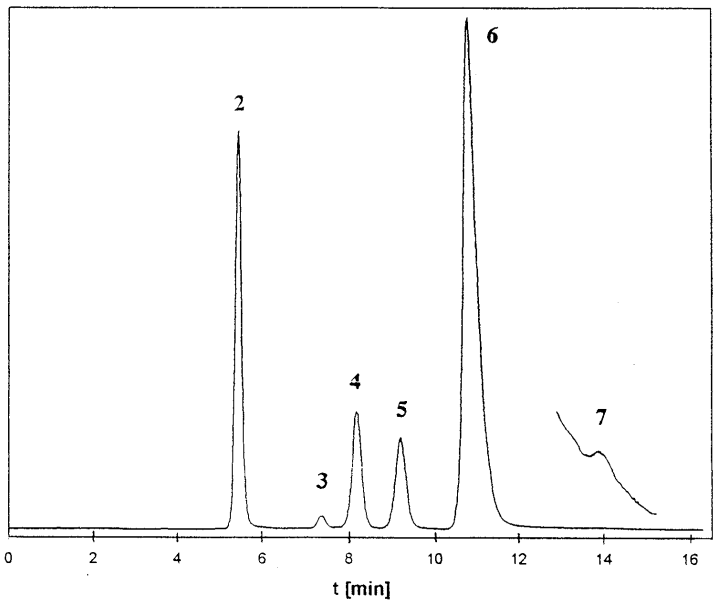
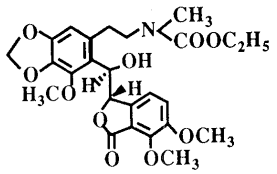


Fig. 1. HPLC Chromatogram of the Reaction Products of α-Narcotine (**1**) with Excess ECF under Reflux
The absorption scale of peak **7** was enlarged.



8

Chart 3

chloro-carbamate **6** is hydrolyzed to the carbinol **7** and the chloro-carbamate **2** affords the carbinol **8**, compounds **6** and **2** must be diastereomers, too. As **6** has 1*S*,9*S* configuration, the configuration of **2** must be 1*R*,9*S*.

Stereochemically pure **6** was refluxed with water and the reaction mixture was directly investigated by ^{1}H-NMR after thorough evaporation: the spectrum shows the corresponding signals for **7** and **8** in a ratio of approximately 8 : 1 (see Experimental). Whilst the carbinol **7** is found in the reaction mixture of α-narcotine (**1**), probably due to the conversion of the chloride **6** by a small amount of water (*vide supra*), the carbinol **8** does not appear in the chromatogram (Fig. 1). These results prove that the main reaction of α-narcotine (**1**; 1*R*,9*S*) with ECF under reflux proceeds stereoselectively to the chloride **6** (1*S*,9*S*), a main component, and successively to the carbinol **7** (1*S*,9*S*). This formal retention from **6** to **7** is obviously due to the generation of a stabilized carbenium ion at C-1 followed by asymmetric induction triggered by the non-affected center of chirality at C-9.

The *E*- and *Z*-enol lactones **4** and **5** were identified by comparison with authentic samples.[1] The structure of **3**, a very small peak in Fig. 1, was confirmed by direct comparison with synthetic **3** prepared from nornarcotine[3] (*N*-demethylnarcotine; –NH instead of –NCH$_3$ in **1**) with ECF. Although similar *N*-desmethyl-*N*-carbethoxyisoquinolines without a benzylic moiety at C-1 were obtained by treatment of *N*-methyl-1,2,3,4-tetrahydroisoquinolines with one molar equivalent of ECF by *N*-demethylation,[4,5] α-narcotine (**1**), containing a benzylic group, did not afford **3** on a preparative scale, but yielded the enol lactones **4** and **5**. Nevertheless, traces of **3** could be detected in the reaction mixture of α-narcotine with ECF by HPLC (Fig. 1).

The EI-MS of **3** shows no molecular ion. The FD- and CI-MS of **3**, however, exhibit MH$^+$ at *m/z* 472 with low intensity, and the CI-MS (NH$_3$) shows an additional peak at *m/z* 489 due to $(M+NH_4)^+$. Two fragment ions in the EI-MS at *m/z* 278 (isoquinoline moiety, 100%) and *m/z* 193 (phthalide moiety, <0.5%) originate from the molecular ion by C-1–C-9-bond cleavage. In contrast to our earlier results,[2] the EI-MS of both *E*/*Z*-isomers **4** and **5** turned out to be identical, because the fragment at *m/z* 278 which was considered to be characteristic of the oily (!) *E*-enol lactone **4** stems from compound **3**, a minor impurity. This fragment, however, is the base peak in the mass spectrum of **3**. As mentioned above, the carbamate **3** arose by ECF-induced *N*-demethylation of **1**. Although some geometrical isomers show individual fragmentation patterns,[6,7] this is apparently not so in the case of **4** (*E*) and **5** (*Z*).

The reaction of β-narcotine was investigated under the reaction conditions described for α-narcotine (**1**). Among the reaction products, the *E*- and *Z*-enol lactones **4** and **5** were virtually undetectable by HPLC. This may be explained by the different stereochemistry.

Experimental

Melting points were taken on a Büchi SMP-20 without correction. Infrared (IR) spectra were acquired on a Nicolet 510 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded with a Bruker ARX 400 (400 MHz) spectrometer in $CDCl_3$ solution with TMS as the internal standard. Mass spectra (EI-, FD-, CI-MS) were obtained on a Finnigan MAT 95 instrument at 70 eV. Optical rotations were measured using a Perkin Elmer 241 MC polarimeter. HPLC (Spectra-Physics 8700, UV detector: Spectra-Physics 8300, λ=254 nm) was performed with a Spherisorb Si column (250×4 mm, 5 μm, Bischoff Analysentechnik, Leonberg, Germany), equipped with a precolumn (Spherisorb Si, 20×4 mm). TLC was done on Kieselgel 60F$_{254}$ aluminum plates (Merck).

Degradation of α-Narcotine (1) with ECF (−)-α-Narcotine (**1**, 0.20 g, 0.5 mmol) in dichloromethane (2 ml) was refluxed with fresh ECF (0.2 ml,

2 mmol) for 4 h. After complete removal of the solvent and excess ECF, the mixture was separated by HPLC using 25% tetrahydrofuran in 75% hexane as an eluent (flow rate, 2.0 ml/min, pressure, 1260 psi). Retention times (min): **2**, 5.48; **3**, 7.41; **4**, 8.21; **5**, 9.22; **6**, 10.70; **7**, 13.90. For nomenclature of (1*R*,9*S*)-**2**, **4**, **5**, (1*S*,9*S*)-**6**, (1*S*,9*S*)-**7**, and (1*R*,9*S*)-**8**: see ref. 1. Instrumental data for **2** and **6**, **4**, **5** and **7**: see ref. 1. The MS of **4** is identical with that of **5**. Products **7** and **8** were identified by HPLC comparison with authentic compounds.[1)]

2: $[\alpha]_D^{25}$ −91° (c=0.1, $CHCl_3$). ^{1}H-NMR δ: 1.19 (t, J=7 Hz, 3H, $-CH_2-C\underline{H}_3$), 2.69—3.28 (m, 4H, $-CH_2-$), 2.75 and 2.84 (2×s, 3H, $-NCH_3$), 3.94, 4.08 and 4.10 (3×s, 9H, $-OCH_3$), 4.07—4.21 (q, J=7 Hz, 2H, $-C\underline{H}_2-CH_3$), 5.00 (br d, 1H, –CH–Cl), 5.95 and 5.97 (AB, J=1.3 Hz, 2H, $-OCH_2O-$), 6.35 (d, J=8 Hz, 1H, –CH–O), 6.38 (s, 1H, aromatic H-5), 7.27 (d, J=8 Hz, 1H, aromatic H-2′), 7.69 (d, J=8 Hz, 1H, aromatic H-3′). EI-MS m/z: 521 (M^+, <0.5), 485 (M−HCl, 4), 418 (6), 382 (14), 328 (21), 294 (11), 221 (18), 220 (100), 193 (18), 116 (15).

6: $[\alpha]_D^{25}$ −164° (c=0.1, $CHCl_3$). ^{1}H-NMR δ: 1.28 (t, J=7 Hz, 3H, $-CH_2-C\underline{H}_3$), 2.34—2.85 (m, 4H, $-CH_2-$), 2.68 and 2.78 (2×s, 3H, $-NCH_3$), 3.83, 4.08 and 4.14 (3×s, 9H, $-OCH_3$), 4.18 (q, J=7 Hz, 2H, $-C\underline{H}_2-CH_3$), 4.94 (br s, 1H, –CH–Cl), 6.02 (s, 2H, $-OCH_2O-$), 6.09 (d, J=8 Hz, 1H, –CH–O), 6.34 (d, J=8 Hz, 1H, aromatic H-2′), 6.38 (s, 1H, aromatic H-5), 6.93 (d, J=8 Hz, 1H, aromatic H-3′). The EI-MS is identical with that of **2**.

Hydrolysis of 6 to 7 The chloride **6** (0.05 g, 0.01 mmol) in acetone (1 ml) was refluxed with water (2 ml) for 2 h. The reaction mixture was extracted with ether, and thorough removal of the solvent *in vacuo* gave a mixture of **7** and **8**, in which **6** was not detected by TLC (chloroform–ether, 3 : 1). This mixture was analyzed by ^{1}H-NMR to show the H-3′ signals as doublets (J=8 Hz) at 7.04 ppm for **7** and 7.54 ppm for **8** with the intensity ratio of 11 : 84.

Preparation of *N*-Desmethyl-*N*-carbethoxynarcotine (3) α-Narcotine (**1**) was oxidized with *m*-chloroperoxybenzoic acid to give narcotine *N*-oxide[8)] (mp 226—228 °C, 85% yield), which was treated with ferric citrate (Sigma) as reported[4)] to yield nornarcotine[9)] (*N*-demethylnarcotine, mp 174—175 °C, 20% yield). Nornarcotine (0.1 g, 2.5 mmol) in anhydrous dichloromethane (2 ml) was refluxed with ECF (0.25 ml, 2.5 mmol) for 2 h. Thorough removal of the solvent, followed by purification by preparative TLC (chloroform–ether, 3 : 1) afforded **3** as colorless crystals (20 mg, 15%). This product was used as an authentic sample for identification of **3** among the reaction products of α-narcotine (**1**). mp 145—146 °C. IR (Nujol): 1705 and 1765 (C=O) cm^{-1}. ^{1}H-NMR (250 MHz) δ: 1.30 (t, J=7 Hz, 3H, $-CH_2-C\underline{H}_3$), 1.70—3.50 (m, 4H, $-CH_2-$), 3.65, 3.88 and 4.02 (3×s, 9H, $-OCH_3$), 4.00—4.20 (q, J=7 Hz, 2H, $-C\underline{H}_2-CH_3$), 4.21 (br s, 1H, methine H-1), 5.60 (d, J=8 Hz, 1H, methine H-9), 5.80 (s, 2H, $-OCH_2O-$), 5.88 (d, J=8 Hz, 1H, aromatic H-3′). 6.35 (s, 1H, aromatic H-5), 6.99 (d, J=8 Hz, 1H, aromatic H-2′). EI-MS m/z: 278 (M − phthalide part, 100), 250 (13), 206 (7), 193 (<0.5), 191 (6). FD-MS m/z: 472 (MH^+), 278 (isoquinoline part), 193 (phthalide part). CI-MS (NH_3) m/z: 472 (MH^+), 489 $(M+NH_4)^+$. HR-MS for $C_{14}H_{16}NO_5$: Calcd 278.10258. Found: 278.10289.

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References

1) Lee D. U., Iwasa K., Kamigauchi M., Takao N., Wiegrebe W., *Chem. Pharm. Bull.*, **39**, 1944 (1991).
2) Lee D. U., Mayer K. K., Wiegrebe W., Takao N., *Arch. Pharm.* (Weinheim), **326**, 251 (1993).
3) Allen A. C., Cooper D. A., Moore J. M., *Anal. Chem.*, **56**, 2940 (1984).
4) *a*) Kraiss G., Nador K., *Tetrahedron Lett.*, **1971**, 57; *b*) Trepanier D. L., Sunder S., *J. Med. Chem.*, **16**, 342 (1973).
5) Lee D. U., Wiegrebe W., *Arch Pharm.* (Weinheim), **319**, 694 (1986).
6) Mandelbaum A., *Mass Spectrom. Rev.*, **2**, 223 (1983).
7) Vairamani M., Saraswathi M., *Mass Spectrom. Rev.*, **10**, 491 (1992).
8) Drummond A. M., McMillan A., *J. Chem. Soc.*, **1926**, 2702.
9) Kerekes P., Bognar R., *J. Prak. Chem.*, **313**, 923 (1971).