Degradation of Some Phthalideisoquinolines with Ethyl Chloroformate-Stereochemical Aspects

Dong-Ung LEE,*[,a] Kinuko IWASA,[b] Miyoko KAMIGAUCHI,[b] Narao TAKAO,[b] and Wolfgang WIEGREBE[c]

College of Natural Science, Dongguk University,[a] Kyongju, Kyongbuk 780-714, Korea, Kobe Women's College of Pharmacy,[b] Kobe 658, Japan, and Faculty of Chemistry and Pharmacy, University of Regensburg,[c] D-8400 Regensburg, Germany. *Received January 18, 1991*

Treatment of phthalideisoquinolines such as α- (1) and β-narcotine (2) as well as β- (3) and α-hydrastine (4) with ethyl chloroformate (ECF) at room temperature afforded, *via* the chloro-carbamates, the corresponding diastereomeric carbinols with high stereoselectivity. Instrumental analyses of each diastereomeric pair indicate that the major isomers derived from α- and β-narcotine as well as from α- and β-hydrastine are enantiomers of each other. The absolute configuration of the major carbinol 6a from α-narcotine (1) was determined by X-ray analysis. The probable difference between the reaction course of α- and β-narcotine is discussed. On the other hand, treatment of α-narcotine with ECF under reflux furnished *Z*-(8) and *E*-(9) enol lactones, while only the *Z*-isomer 12 could be isolated from the degradation of β-hydrastine (3) even at room temperature.

Keywords α-narcotine; β-narcotine; α-hydrastine; β-hydrastine; ethyl chloroformate; diastereoselectivity; enantiomer; diastereomeric carbinol; enol lactone; X-ray analysis; absolute configuration

Phthalideisoquinolines such as (−)-α-narcotine (**1**), (−)-β-narcotine (**2**), (−)-β-hydrastine (**3**), and (−)-α-hydrastine (**4**) possess two asymmetric centers: at C-1 of the tetrahydroisoquinoline nucleus and at C-9 of the γ-lactone ring (Charts 1 and 4). The ring cleavage of one or both cyclic systems in the above phthalideisoquinolines has been accomplished by various methods, *e.g.* Hofmann degradation,[1,2] or using benzyl bromide,[3] *m*-chloroperoxybenzoic acid,[4] or phenyl chloroformates,[5,6] to furnish the corresponding enol lactones (stilbenes) or keto acids. Some of these ring-cleaved phthalideisoquinolines are known to be present in nature as secophthalideisoquinolines.[7] This paper deals with the reactions of α- and β-narcotine as well as α- and β-hydrastine with ethyl chloroformate (ECF).

A. Degradation of α- and β-Narcotine with Ethyl Chloroformate When (−)-α-narcotine (**1**) was treated with ECF at room temperature, the chloro-carbamate **5** was obtained as a colorless crystalline material, which, however, could not be completely purified (Chart 1). Benzyl chlorides

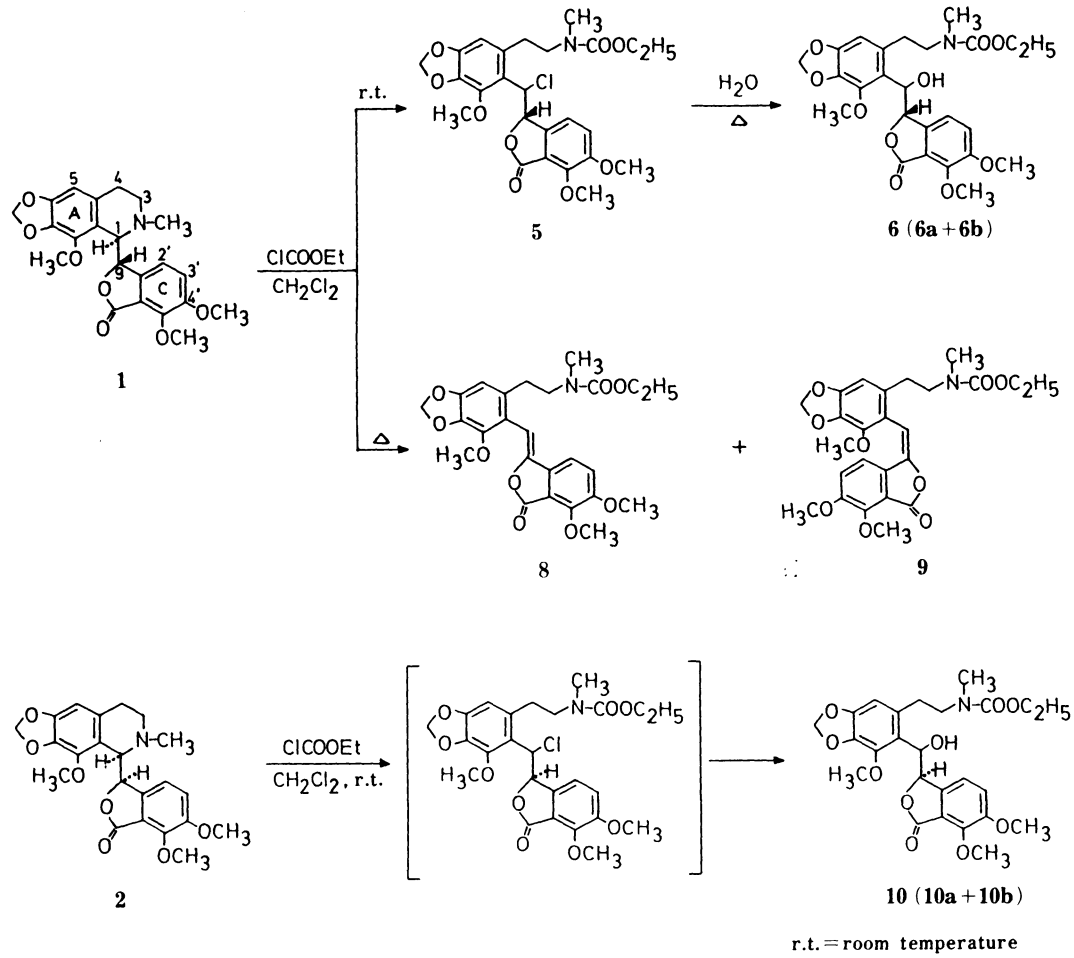


Chart 1

similar to **5** are generally known to be unstable, although a species of this type could be isolated by using special reaction conditions and work-up techniques.[8] Compound **5** was found to be contaminated with a small amount of **6a**, the main diastereomer of the carbinol **6**, as indicated by the doublet of H-3′ at 7.04 ppm, though its field disorption (FD)- and chemical ionization-mass spectrum (CI-MS) did not show peaks due to **6**. On account of the lability of the chloro-carbamate **5** (see below), we can not obtain data indicating the stereochemistry at C-1 of **5**. With the exception of the signals due to the carbinols **6a** and **6b**, (H-3′ at $\delta = 7.54$ ppm), there are no signals in the proton-nuclear magnetic resonance (^{1}H-NMR) spectrum of **5** pointing to the presence of a diastereomer. Nevertheless, the questions of the absolute configuration and stereochemical purity of **5** remain open. The same holds true for the chloro-carbamate **13** obtained from β-hydrastine **3** (see below).

When we tried to purify the chloro-carbamate **5** by column chromatography, a mixture of **5** and carbinol **6** (1 : 1) was obtained. Besides **6a**, the diastereomeric carbinol **6b** was formed in a trace amount (H-3′-doublet at $\delta = 7.54$ ppm). These assignments were established by spiking the mixtures with authentic compounds.

The crude chloro-carbamate **5** containing a small amount of **6a** was refluxed with water to yield **6a** and in a ratio of approximately 13 : 1 (^{1}H-NMR). This means that the conversion of α-narcotine (**1**) with ECF into the carbinol **6** *via* the chloro-carbamate **5** is highly stereoselective; therefore **6a** (major diastereomer) could be separated by chromatographic methods, showing an optical activity of $[\alpha]_D$ −44°.

On the other hand, when (−)-β-narcotine (**2**) was converted into the corresponding carbinol **10** under the conditions used for α-narcotine (**1**), the diastereomer ratio was approximately 5 : 1 for **10a** and **10b** (Chart 1). Furthermore, the optical activity of **10a** exhibits an opposite value ($[\alpha]_D$ +44°) to that of **6a** ($[\alpha]_D$ −44°), though its ^{1}H-NMR and other instrumental data are identical with those of **6a**, indicating that **6a** and **10a** are enantiomers of each other. These results point toward different stereochemical courses in the degradation of α- and β-narcotine with ECF, because the absolute configurations of α- and β-narcotine are known to be 1*R*,9*S* and 1*R*,9*R* respectively,[9,10] that is, the stereochemistry at C-1 in both narcotine diastereomers is the same.

The absolute configuration of **6a** was established by X-ray analysis. The crystal structure is presented in Fig. 1.

This X-ray determination indicates that the conformation of **6a** is *threo*. Therefore, the absolute configuration of **6a** is 1*S*,9*S*, because the absolute configuration of α-narcotine (**1**) is 1*R*,9*S* and the 9*S* configuration is not affected during the reaction. This result apparently proves an inversion in the overall two-step process **1**→**5**→**6a**. Because **6a** from α-narcotine (**1**) and **10a** from β-narcotine (**2**) are enantiomers of each other, the absolute configuration of **10a** corresponds to 1*R*,9*R*, which is identical with that of the starting material, β-narcotine. This fact indicates that the overall reaction includes a retention of configuration.

As already stated (see above) we cannot determine the absolute configuration of the chloro-carbamate **5**. Therefore, we cannot make definite statements concerning the reaction mechanism: a carbenium ion intermediate, substituted by Cl^- or water (with deprotonation), controlled by the non-affected center of chirality at C-9 (asymmetric induction) may produce the chloro-carbamate **5** and the carbinol **6**.

The high diastereoselectivity in the two-step reactions of α-narcotine (**1**) and β-narcotine (**2**) to give the carbinols **6** and **10**, respectively, points at least towards a partition of S_N2 reactions. This also holds true for the reactions of α- and β-hydrastine, **4** and **3**, resectively (see below).

Having ascertained the structure and stereochemistry of the carbinol **6a** and, therefore, of its enantiomer **10a**, we

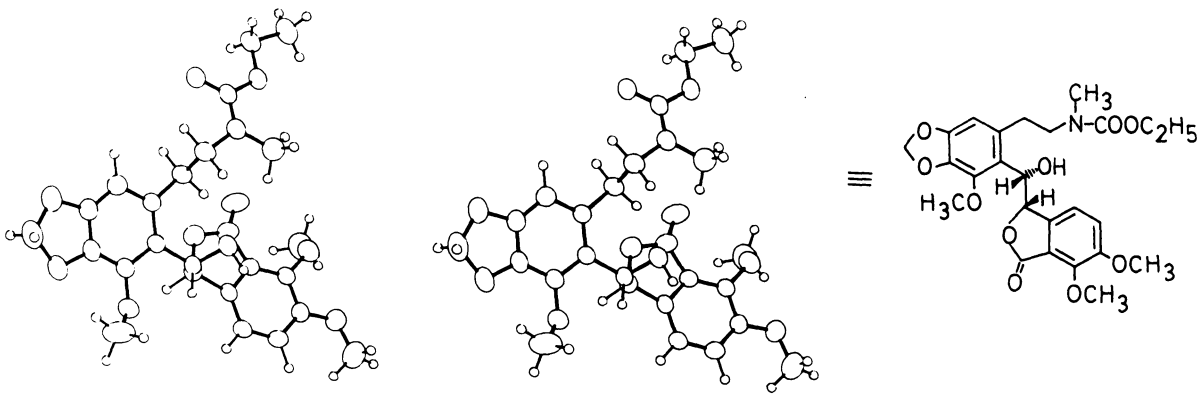


Fig. 1. Stereoscopic View of (1*S*,9*S*)-**6a**

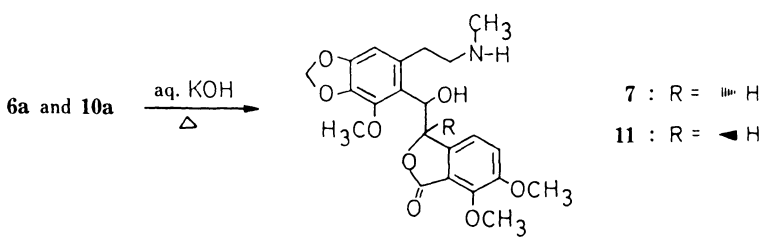


Chart 2

hydrolyzed **6a** and **10a** to the corresponding enantiomeric amines **7** and **11**. When α-narcotine (**1**) was treated with ECF under reflux, not at room temperature, two isomers *Z*-(**8**, 70%), which is thermodynamically more stable, and *E*-lactone (**9**, 4%) were produced (Chart 1). The stereochemistry of **8** and **9** could easily be confirmed by comparison with that of similar *E*/*Z*-isomers whose configurations have been established by nuclear magnetic resonance (NMR)[2] or by X-ray analysis.[5] Shamma and coworkers[2] did not obtain any enol lactone, but obtained the keto acid narceine (**16**) from mild Hofmann degradation (basic conditions) of α-narcotine. They suggested that hydrolysis of an intermediate enol lactone (CH_3 instead of $COOC_2H_5$ in **8**) must occur with great ease. This may, in our case, explain why an analogous keto acid was not formed in our ethyl chloroformate degradation (non-basic conditions) either at room temperature or under reflux conditions (*vide supra*).

The reason why α-narcotine does not form *E*/*Z*-isomers at room temperature may be the steric effect of its C-8 methoxy group, which prevents an anti-periplanar arrangement suitable for easy HCl elimination. In addition, the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum (Table II) of *E*-isomer **9** is contaminated with signals of the *Z*-isomer **8**, this may result from partial isomerization under the measuring conditions (50 °C for 5 h in $CDCl_3$).

Photoisomerization, as is usual in similar stilbenes,[11] was excluded. Moreover, oily **9** crystallized even upon grinding without any contact with solvent, being converted into crystalline **8**. The chemical shifts for H-2′ and H-3′ of the *Z*- (**8**) and *E*-isomer (**9**) are apparently different from each other (Table I). The H-2′ an H-3′ doublets (J=8 Hz) of the *E*-isomer **9** appear more upfield (δ=6.66 and 7.07 ppm) than those of the *Z*-isomer **8** (δ=7.49 and 7.28 ppm), since H-2′ and H-3′ in the *E*-isomer **9** are closer to the shielding zone of the aromatic ring A than the same protons in the *Z*-isomer **8**. The mass spectra of the enol lactones **8** and **9** are not identical. The fragment peaks at m/z=278, 250 and 206, respectively, in the spectrum of the *E*-isomer **9** are not found in that of the *Z*-isomer **8**. For this fragmentation, a direct bond cleavage at the aromatic ring after two 1,5-H-shifts may be suggested (Chart 3) (for fission of the double bond after electron impact in similar stilbenes, see ref. 12).

B. Degradation of α- and β-Hydrastine with Ethyl Chloroformate Degradation of (−)-β-hydrastine (**3**) and (−)-α-hydrastine (**4**) with ECF is somewhat different from that of α-narcotine (**1**) under the same conditions. When β-hydrastine (**3**) was treated with ECF at room temperature as described for **1** to **6**, the product mixture consists of three components on thin layer chromatography (TLC) (Chart 4).

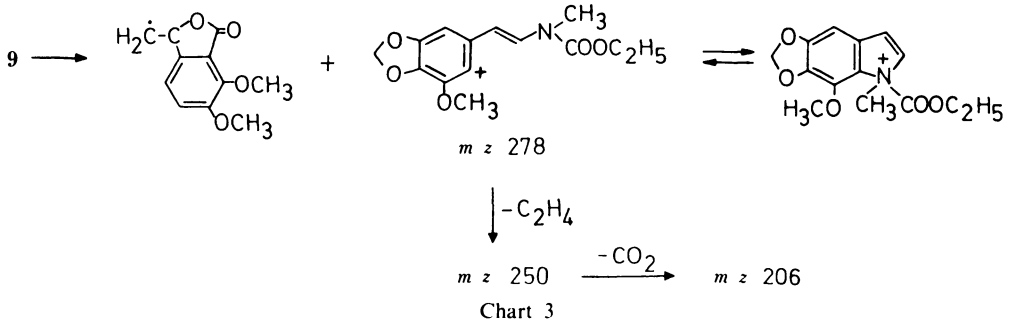
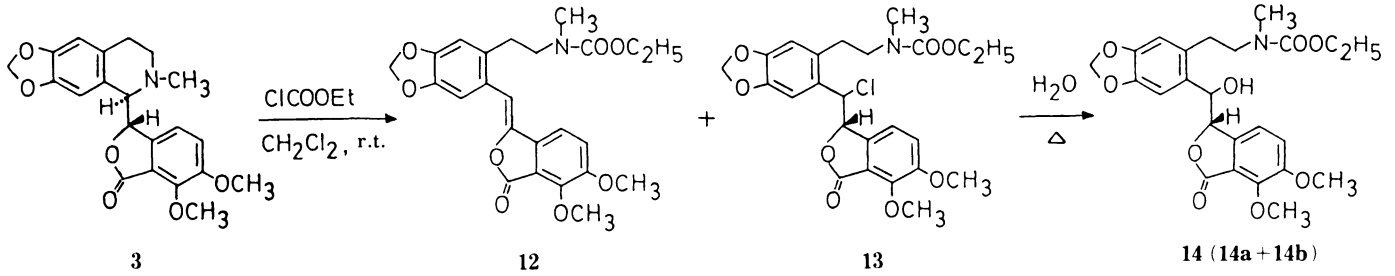
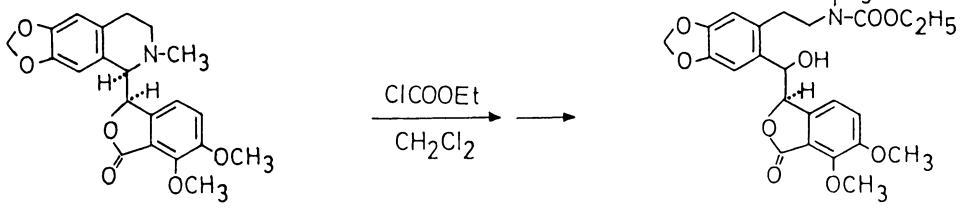


Chart 3



3 **12** **13** **14 (14a+14b)**



4 **15 (15a+15b)**

Chart 4

TABLE I. ^{1}H-NMR Chemical Shifts for Carbinols and Enol Lactones[a]

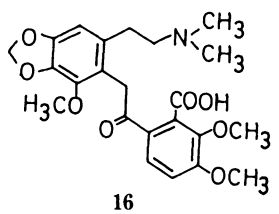
	8	9	6a, 10a	7, 11[b]	10b	12	14b, 15b	14a, 15a
$-CH_2-\underline{CH}_3$	1.15[c]	1.22[c]	1.23[c]	—	1.22[c]	1.22[c]	1.11[c]	1.18[c]
$N-CH_3$	2.76	2.78	2.79	2.27	2.82	2.89	2.86	2.79
$-CH_2-$	2.79[c]	2.72[c]	2.44—2.72[d]	2.54—2.67[d]	2.57—2.88[d]	2.94[c]	2.61—2.80[d]	2.58[c]
$-CH_2-N$	3.39[c]	3.30[c]	2.88—3.40[d]	2.94—3.15[d]	3.22—3.46[d]	3.43[c]	3.15—3.40[d]	3.27[c]
$-\underline{CH}_2-CH_3$	3.98[e]	4.10[e]	4.12[e]	—	4.06—4.24[f]	4.16[e]	4.00[e]	4.08[e]
$3\times OCH_3$	3.94	3.88	3.85	3.87	3.96	3.97	3.92	3.86
	4.14	4.14	4.04	4.01	4.12	4.18	4.09	4.06
	4.01	3.89	4.08	4.11	4.18	—	—	—
$-OCH_2O-$	5.93	6.01	6.02, 6.04[g]	5.97	5.96, 5.98[g]	6.00	5.97	5.98
H-1	6.36	6.44	4.82[h]	5.15[i]	4.74[j]	6.66[h]	4.96[i]	5.05[j]
H-9	—	—	5.86[i]	5.72[i]	5.70[i]	—	5.44[i]	5.48[i]
H-5	6.48	6.57	6.43	6.45	6.41	6.72	6.64	6.66
H-2′	7.49[i]	6.66[i]	6.36[h]	6.51[i]	7.25[i,k]	7.77[h,k]	7.23[h,k]	6.43[h]
H-3′	7.28[i]	7.07[i]	7.04[i]	7.07[i]	7.51[i,k]	7.32[i]	7.22[h,k]	7.06[i]
H-8	—	—	—	—	—	7.73[h,k]	7.07	7.04

a) At 200 MHz, 50 C, $CDCl_3$, δ = ppm. Some chemical shifts were assigned by using 2D-NMR (COSY and HETCOR). *b*) Chemical shifts for OH and NH protons of **11**: 3.24 ppm (OH + NH, br, recorded at 25 °C). *c*) Triplet, J = 7.0 Hz. *d*) Multiplet. *e*) Quartet, J = 7.0 Hz. *f*) Hidden in OCH_3 protons. *g*) AB, J = 1.3—1.5 Hz. *h*) Broad singlet. *i*) Doublet, J = 8.0 Hz. *j*) Triplet, J = 7.0 Hz; doublet (J = 8.0 Hz) after D_2O exchange. *k*) Assignments may be reversed.

TABLE II. ^{13}C-NMR Chemical Shifts for CH Carbons for Carbinols and Enol Lactones

	6a	8	9	10b	12	14a	14b
C-1	73.4	99.6	103.1	72.7	101.6	72.2	71.1
C-5	105.3	104.1	104.1	105.3	110.4	108.0	107.4
C-8	—	—	—	—	110.0	110.0	110.1
C-9	82.5	—	—	80.3	—	83.0	81.4
C-2′	117.8	115.2	118.2[a]	118.3[a]	115.4	118.0[a]	118.9[a]
C-3′	119.3	120.3	119.7[a]	119.9[a]	120.6	119.4[a]	119.6[a]

a) Assignments may be reversed.



16

a) The upper fluorescent component shows characteristic absorptions with high intensity and long wavelength in its ultraviolet (UV) spectrum: λ_{max} nm (log ε) = 227 (4.27), 240 (sh), 307 (4.09), 378 (4.22). It follows that this compound must have the *Z* geometry, which is identical with that of natural *N*-methylhydrastine [CH_3 instead of $COOC_2H_5$ in **12**, λ_{max} nm (log ε) = 228 (4.33), 240 (sh, 4.22), 301 (4.09), 380 (4.23)], so confirming the structure of the enol lactone **12**. Enol lactones (*E*/*Z*-isomers) were derived from β-hydrastine (**3**) by various methods; among them, the mild Hofmann degradation of **3** affords both *Z*- and *E*-enol lactones.[2] However, other authors[5] using phenyl chloroformate under reflux did not mention the *E*-isomer. We also could not isolate the *E*-isomer from ethyl chloroformate degradation of **3**, but obtained the *Z*-isomer only. b) The main fraction on TLC was separated and identified as a chloro-carbamate **13** (see Experimental). c) The minor component on TLC was found to be the carbinol **14**. The above crude reaction mixture containing **12**, **13**, and **14** was heated with water to yield the corresponding diastereomeric carbinols **14a** and **14b** in a ratio of approximately 3 : 1. This is very different from the ratio of 13 : 1 for **6a** and **6b** derived from α-narcotine (**1**). Considering the same absolute configurations (1*R*,9*S*) of α-narcotine (**1**) and β-hydrastine (**3**), this drastic difference in stereoselectivity may stem from the C-8 methoxy group in α-narcotine, which is absent in β-hydrastine. Whaley and Meadow[13] reported that the action of ECF upon hydrastine under Schotten–Baumann conditions afforded meconine and *N*-carbethoxyhydrastinine. Similarly, meconine and *N*-carbethoxycotarnine were formed from narcotine.[13] Finally, the conversion of α-hydrastine (**4**) afforded **15a** and **15b** in a ratio of approximately 2 : 1. This result is also significantly different from the ratio of 5 : 1 for **10a** and **10b** derived from β-narcotine, whose absolute configuration is identical with that of α-hydrastine.[9] Several instrumental analyses also proved **14a** and **15a** as well as **14b** and **15b** to be enantiomers of each other.

Experimental

Melting points were taken on a Kofler hot stage apparatus, and are uncorrected. Infrared (IR) spectra were recorded on an EPI-G2 (Hitachi) spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on Varian XL-200 (200 MHz) and VXR-500S (500 MHz) spectrometers in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. Mass spectra were determined on a Hitachi M80 instrument at 75 eV. The chemical ionization mass spectra were obtained by using isobutane as the ionizing gas. Optical rotations were measured using a DIP-SL (Jasco) polarimeter. Circular dichroism (CD) and UV spectra were determined on a Jasco ORD/UV-5 spectrometer. Microanalyses were performed by the Microanalytical Laboratory in Kobe Women's College of Pharmacy, Japan. TLC and preparative TLC were done on Silicagel 60F-254 glass plates.

(−)-3-{[2-(*β*-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]chloromethyl}-6,7-dimethoxy-1(3*H*)-isobenzofuranone (5) α-Narcotine (**1**), (0.41 g, 1 mmol) in anhydrous dichloromethane (2 ml) was stirred with fresh ECF (0.4 ml, 4 mmol) at room temperature for 5 h. Thorough removal of the solvent and the excess ECF gave **5** as a colorless crystalline material, which was not further purified. $[\alpha]_D^{25}$ −26° ($CHCl_3$). IR (Nujol): 1700, 1765 (CO) cm^{-1}. ^{1}H-NMR (signals of **6** are omitted, 200 MHz at 50 °C) δ: 1.26 (t, J = 7.0 Hz, 3H, $-CH_2-\underline{CH}_3$), 2.32—3.38 (m, 4H, $-CH_2-$), 2.76 and 2.80 (2 × s, 3H, $-NCH_3$), 3.84, 4.10 and 4.12 (3 × s, 9H, $-OCH_3$), 4.14 (q, J = 7.0 Hz, 2H, $-\underline{CH}_2-CH_3$), 5.02 (br s, 1H, -CH-Cl), 6.02, 6.06 (AB, J = 1.3 Hz, 2H, $-OCH_2O-$), 6.14 (d, J = 8.0 Hz, 1H, -CH-O-), 6.34 (d, J = 8.0 Hz, 1H,

aromatic), 6.44 (s, 1H, aromatic), 6.96 (d, J=8.0 Hz, 1H, aromatic). MS m/z (relative intensity, %): 382 (69), 338 (29), 328 (21), 310 (26), 292 (29), 236 (30), 220 (100), 193 (27), 179 (22), 116 (60). FD-MS m/z: 521 ($M^+\cdot$), 485 (M−HCl). CI-MS m/z: 522 (M+1).

(−)-3-{[2-(β-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]hydroxymethyl}-6,7-dimethoxy-1(3*H*)-isobenzofuranone (6a and 10b) and (+)-(10a) α-Narcotine (**1**) or β-narcotine (**2**)[10] (4.13 g, 0.01 mol) was dissolved in dichloromethane (10 ml) and stirred with ECF (4 ml, 0.04 mol) at room temperature for 5 h. The solvent and the excess ECF were thoroughly removed to give the crude products, which were refluxed with water for 5 h, then cooled reaction mixture was extracted with dichloromethane. Removal of the solvent gave the diastereomeric carbinol **6** or **10**, respectively. Preparative TLC with chloroform–ether (1 : 1) provided **6a** from **1**, and **10a** and **10b** from **2**. Compound **6b** could not be obtained in a sufficient amount for analyses. **6a**: mp 98—99 °C, $[\alpha]_D^{25}$ −44° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{29}NO_{10}$: C, 59.62; H, 5.80; N, 2.78. Found: C, 59.54; H, 5.72; N, 2.90. IR (Nujol): 1670 and 1760 (CO), 3350 (OH) cm^{-1}. UV λ_{max} nm (log ε): 212 (4.62), 292 (sh), 309 (3.49). CD (c=0.001, methanol) Δε (nm): −1.43 (310), +0.17 (283), −1.14 (260), +1.26 (249), −13.16 (230). MS m/z (relative intensity, %): 486 ($M^+\cdot$−OH, 0.4), 310 (81), 282 (11), 236 (100), 220 (8), 207 (65), 206 (34), 194 (24), 193 (30), 179 (82), 165 (14), 116 (62). CI-MS m/z: 486 ($M^+\cdot$−OH). ^{1}H- and ^{13}C-NMR: see Tables I and II. Crystal data: $C_{25}H_{29}NO_{10}$; M_r=503.51; crystal system, monoclinic; space group, $P2_1$; cell constants, a=8.377 Å, b=10.707 Å, c=14.349 Å, β=101.85; V=1259.57 Å^3; Z=2; D_x=1.328 g·cm^{-3}; D_m=1.316 g·cm^{-3}; $F(000)$=532; λ=1.5405 Å.

10a: mp 98—99 °C, $[\alpha]_D^{25}$ +44° (c=0.5, $CHCl_3$). *Anal.* Calcd as above. Found: C, 59.37; H, 5.80; N, 2.72. Other instrumental data are identical with those of **6a**. **10b**: mp 133—134 °C, $[\alpha]_D^{25}$ −18° (c=0.5, $CHCl_3$). *Anal.* Calcd as above. Found: C, 59.35; H, 5.90; N, 2.86. IR (Nujol): 1705, 1780 (CO), 3400 (OH) cm^{-1}. UV λ_{max} nm (log ε): 225 (4.26), 290 (3.33), 311 (3.44). MS m/z (relative intensity, %): 486 ($M^+\cdot$−OH, 0.2), 310 (31), 282 (5), 236 (55), 220 (4), 207 (40), 206 (69), 194 (25), 193 (14), 179 (42), 165 (25), 116 (100). ^{1}H- and ^{13}C-NMR: see Tables I and II.

(*Z*)-3-[2-(β-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-6-methoxy-4,5-methylenedioxybenzylidenyl]-6,7-dimethoxy-1(3*H*)-isobenzofuranone (8) and (*E*)-(9) α-Narcotine (**1**) (4.13 g, 0.01 mol) in dichloromethane (10 ml) was treated with ECF (4 ml, 0.04 mol) under reflux for 4 h. The solvent and the excess ECF were thoroughly removed by evaporation *in vacuo*, then the crude product was separated by column chromatography with chloroform–ether (4 : 1) to furnish **8** (pale yellow crystals, second fraction, major) and **9** (yellow oil, 200 mg, first fraction, minor). Attempts to crystallize the oily **9** resulted in its easy conversion to **8**. **8**: mp 168—169 °C (ether). *Anal.* Calcd for $C_{25}H_{27}NO_9$: C, 61.87; H, 5.56; N, 2.89. Found: C, 61.75; H, 5.62; N, 2.85. IR (Nujol): 1705, 1775 (CO) cm^{-1}. UV λ_{max} nm (log ε): 222 (4.54), 285 (4.17), 355 (4.20). MS m/z (relative intensity, %): 485 ($M^+\cdot$, 12), 383 (24), 382 (100), 369 (12), 292 (17), 218 (14), 193 (34), 116 (90). ^{1}H- and ^{13}C-NMR: see Tables I and II. **9**: yellow oil. IR (neat): 1680, 1765 (CO) cm^{-1}. UV λ_{max} nm (log ε): 216 (4.76), 280 (sh), 348 (4.16). MS m/z (relative intensity, %): 485 ($M^+\cdot$, 9), 383 (24), 382 (100), 369 (12), 292 (18), 279 (15), 278 (81), 250 (20), 218 (16), 206 (11), 193 (42), 116 (92). ^{1}H- and ^{13}C-NMR: see Tables I and II.

(−)-3-{[2-(β-*N*-Methylaminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]hydroxymethyl}-6,7-dimethoxy-1(3*H*)-isobenzofuranone (7) and (+)-(11) Compound **6a** or **10a** (0.2 g, 0.4 mmol), was dissolved in ethanol (20 ml) and refluxed with 50% aqueous KOH (10 ml) for 12 h. The reaction mixture was diluted with water and neutralized with 2 N HCl, then extracted with chloroform. After removal of the solvent, the crude oily product was purified by preparative TLC with methanol to provide **7** or **11**, respectively. **7**: $[\alpha]_D^{25}$ −27° (c=0.38, $CHCl_3$). IR (neat): 1620, 1760 (CO), 2700—3050 (NH), 3500 (br, OH) cm^{-1}. MS m/z (relative intensity, %): 431 ($M^+\cdot$, 4), 238 (100), 207 (74). CI-MS m/z: 432 (M+1). ^{1}H-NMR: see Table I. **11**: $[\alpha]_D^{25}$ +24° (c=0.5, $CHCl_3$). IR, MS, and ^{1}H-NMR spectrum are identical with those of **7**.

(*Z*)-3-[2-(β-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-4,5-methylenedioxybenzylidenyl]-6,7-dimethoxy-1(3*H*)-isobenzofuranone (12) and 3-{[2-(β-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-4,5-methylenedioxyphenyl]-chloromethyl}-6,7-dimethoxy-1(3*H*)-isobenzofuranone (13) Treatment of β-hydrastine (**3**) with ECF as described for **1** to **5** yielded **12** and **13**, which were separated by preparative TLC with benzene–ether (4 : 1).

12: yellow needles, mp 144 °C (ether). *Anal.* Calcd for $C_{24}H_{25}NO_8$: C, 63.30; H, 5.54; N, 3.08. Found: C, 63.44; H, 5.46; N, 2.98. IR (Nujol): 1680, 1775 (CO) cm^{-1}. UV λ_{max} nm (log ε): 227 (4.27), 240 (sh), 307 (4.09), 378 (4.22). MS m/z (relative intensity, %): 455 ($M^+\cdot$, 44), 353 (16), 352 (66), 339 (27), 311 (18), 262 (10), 193 (23), 116 (100). ^{1}H- and ^{13}C-NMR: see Tables I and II. **13**: IR (neat): 1680, 1760 (CO) cm^{-1}. ^{1}H-NMR (200 MHz at 50 °C) δ: 1.28 (t, J=7.0 Hz, 3H, $-CH_2-C\underline{H}_3$), 2.60—3.40 (m, 4H, $-C\underline{H}_2-$), 2.87 (s, 3H, $-NCH_3$), 3.93 and 4.09 (2×s, 6H, $-OCH_3$), 4.18 (q, J=7.0 Hz, 2H, $-C\underline{H}_2-CH_3$), 5.20—5.70 (br d, 2H, –OCH–, –CH–Cl), 5.99 (s, 2H, $-OCH_2O-$), 6.64—7.20 (m, 4H, aromatic).

(−)-3-{[2-(β-*N*-Ethoxycarbonyl-*N*-methylaminoethyl)-4,5-methylenedioxyphenyl]hydroxymethyl}-6,7-dimethoxy-1(3*H*)-isobenzofuranone (14a and 15a) and (+)-(14b and 15b) Compounds **14a**, **14b**, **15a** and **15b** were obtained from the corresponding β-hydrastine (**3**) or α-hydrastine (**4**)[14] by the procedure described for **1** to **6a**. Purification was achieved by preparative TLC with benzene–ether (4 : 1).

14a: mp 135—136 °C (ether). $[\alpha]_D^{25}$ −9° (c=0.5, $CHCl_3$). *Anal.* Calcd for $C_{24}H_{27}NO_9$: C, 60.87; H, 5.74; N, 2.96. Found: C, 60.61; H, 5.79; N, 2.91. IR (Nujol): 1690, 1760 (CO), 3400 (OH) cm^{-1}. UV λ_{max} nm (log ε): 211 (4.67), 235 (sh), 295 (3.89), 310 (sh). MS m/z (relative intensity, %): 456 ($M^+\cdot$ −OH, 1), 280 (61), 206 (100), 194 (35), 177 (60), 149 (26), 116 (40). CI-MS m/z: 474 (M+1). ^{1}H- and ^{13}C-NMR: see Tables I and II. **14b**: $[\alpha]_D^{25}$ +8° (c=0.5, $CHCl_3$). IR (neat): 1670, 1760 (CO), 3400 (br, OH) cm^{-1}. UV λ_{max} nm (log ε): 216 (4.84), 235 (sh), 295 (4.38), 310 (sh). EI- and CI-MS are identical with those of **14a**. ^{1}H- and ^{13}C-NMR: see Tables I and II. **15a**: mp 135—136 °C (ether). $[\alpha]_D^{25}$ +9° (c=0.5, $CHCl_3$). *Anal.* Calcd as above. Found: C, 60.60; H, 5.72; N, 3.08. Other instrumental data are identical with those of **14a**. **15b**: $[\alpha]_D^{25}$ −8° (c=0.5, $CHCl_3$). Other instrumental data are identical with those of **14b**.

Acknowledgement We thank Prof. T. Ishida, Osaka College of Pharmacy, Japan, for X-ray analysis.

References

1) M. Freund and G. B. Frankforter, *Justus Liebigs Ann. Chem.*, **277**, 20 (1893).
2) G. Blasko, V. Elango, B. Sener, A. J. Freyer, and M. Shamma, *J. Org. Chem.*, **47**, 880 (1982).
3) W. Klötzer, S. Teitel, and A. Brossi, *Monatsh. Chem.*, **103**, 1210 (1972).
4) K. Iwasa, M. Kamigauchi, M. Sugiura, and N. Takao, *J. Nat. Prod.*, **50**, 1083 (1987).
5) W. Klötzer, S. Teitel, and A. Brossi, *Helv. Chim. Acta*, **55**, 2228 (1972).
6) H. L. Holland, M. Curcumelli-Rodostamo, and D. B. Maclean, *Can. J. Chem.*, **54**, 1472 (1976).
7) G. Blasko, D. J. Gula, and M. Shamma, *J. Nat. Prod.*, **45**, 105 (1982).
8) D. U. Lee and W. Wiegrebe, *Arch. Pharm.* (Weinheim, Ger.), **319**, 694 (1986).
9) K. Bláha, J. Hrbek Jun, J. Kovář, L. Pijewska, and F. Šantavý, *Coll. Czech. Chem. Commun.*, **29**, 2328 (1964).
10) A. R. Battersby and H. Spencer, *J. Chem. Soc.*, **1965**, 1087.
11) S. von Angerer, E. Eibler, D. U. Lee, and W. Wiegrebe, *Sci. Pharm.*, **57**, 1 (1989); A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, **1962**, 3526.
12) K. K. Mayer, S. Prior, and W. Wiegrebe, *Monatsh. Chem.*, **117**, 533 (1986).
13) W. M. Whaley and M. Meadow, *J. Org. Chem.*, **19**, 666 (1954).
14) M. A. Marshall, F. L. Pyman, and R. Robinson, *J. Chem. Soc.*, **1934**, 1315.