Degradation of Some Phthalideisoquinolines with Ethyl Chloroformate-Stereochemical Aspects

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Treatment of phthalideisoquinolines such as α- (1) and β-narcotine (2) as well as α- (3) and β-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-chloroperbenzoic 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 secoephthalideisoquinolines.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](chart1.png)

1991 Pharmaceutical Society of Japan
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. 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 δ = 7.54 ppm), there are no signals in the proton-nuclear magnetic resonance (1H-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 δ = 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 (1H-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 [α]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 ([α]D = -44°) to that of 6a ([α]D = +44°). Therefore, the absolute configuration of 6a is 1S,9S, because the absolute configuration of α-narcotine (1) is 1R,9S and the 9S configuration is not affected during the reaction. This result apparently proves an inversion in the overall two-step process 1→5→6a. Because 6a and 10a are enantiomers of each other, the absolute configuration of 10a corresponds to 1R,9R, 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- and β-narcotine (1) and β-narcotine (2) to give the carbinols 6 and 10, respectively, points at least towards a partition of SN2 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
hydrolyzed 6a and 10a to the corresponding enantiomeric amines 7 and 11. When \( \alpha \)-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) or by X-ray analysis. Shamma and coworkers did not obtain any enol lactone, but obtained the keto acid narceine (16) from mild Hofmann degradation (basic conditions) of \( \alpha \)-narcotine. They suggested that hydrolysis of an intermediate enol lactone (CHO instead of COOCH\(_2\)H\(_5\) 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 \( \alpha \)-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 CDC\(_3\)).

Photoisomerization, as is usual in similar stilbenes, 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 (\( \delta = 6.66 \) and 7.07 ppm) than those of the Z-isomer 8 (\( \delta = 7.49 \) 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 \( \alpha \)- and \( \beta \)-Hydrastine with Ethyl Chloroformate Degradation of (-)-\( \beta \)-hydrastine (3) and (-)-\( \alpha \)-hydrastine (4) with ECF is somewhat different from that of \( \alpha \)-narcotine (1) under the same conditions. When \( \beta \)-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).
chloro-carbamate 13 (see Experimental), c) The minor
heated with water to yield the corresponding diastereomeric
main fraction on TLC was separated and identified as a

3.24 ppm (OH + NH, br, recorded at 25°C).

2) of 11: hydrastine (3) by various methods; among them, the mild
in natural JV-methylhydrastine [CH
must have the Z geometry, which is identical with that of

Assignments may be reversed.

- OCH

enol lactones

a) Assignments may be reversed.

The upper fluorescent component shows characteristic
absorptions with high intensity and long wavelength in its
ultraviolet (UV) spectrum: 
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 a-narcotine (1). Considering the same absolute
configurations (1R,9S) of a-narcotine (1) and \( \beta \)-hydrastine
(3), this drastic difference in stereoselectivity may stem from the
C-8 methoxy group in \( \alpha \)-narcotine, which is absent in
\( \beta \)-hydrastine. Whaley and Meadow\(^{13}\) reported that the
action of ECF upon hydrastine under Schotten–Baumann
conditions afforded meconine and N-carbethoxyhydrastine.
Similarly, meconine and N-carbethoxytocatine were
formed from narcotine.\(^{13}\) Finally, the conversion of \( \alpha \)-
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
\( \beta \)-narcotine, whose absolute configuration is identical with that of \( \alpha \)-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-5005 (500 MHz) spectrometers in CDCl
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 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.

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(0.4), 310 (81), 282 (11), 236 (30), 220 (100), 193 (27), 179 (22), 166 (60). FD-MS m/z: 521 (M+), 485 (M-HCl). CI-MS m/z: 522 (M+).  

(-)-3-[2-(β-N-Ethoxycarbonyl-N-methylamino)ethyl]-6-methoxy-4,5-methylenedioxyphenyl]-6,7-dimethoxy-1(3H)-isobenzofuranone (6a and 10b) and (+)-10a α-Narotine (1) or β-narotine (2) (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 mixture (66), 339 (27), 311 (18), 262 (10), 193 (23), 116 (100). H+ and 13C-NMR: see Tables I and II.  

(+)-10b: [a]D5 153—136°C (ether).  

Anal. Calcd for C26H24NO9: M, 503.51; M+, 502.49; M-HCl, 486. 1H and 13C-NMR: see Tables I and II.  

(+)-3-[2-(β-N-Ethoxycarbonyl-N-methylamino)ethyl]-6-methoxy-4,5-methylenedioxyphenyl]-6,7-dimethoxy-1(3H)-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 CHCl3. After the extraction of the solvent, the crude oil product was purified by preparative TLC with methanol to provide 7 or 11, respectively.  

[2]D5 27° < 0.8 (c = 0.38, CHCl3). IR, MS, and 1H-NMR spectrum are identical with those of 7.  

(-)-3-[2-(β-N-Methylamino)ethyl]-6-methoxy-4,5-methylenedioxyphenyl]-6,7-dimethoxy-1(3H)-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 CHCl3. After the extraction of the solvent, the crude oil product was purified by preparative TLC with methanol to provide 7 or 11, respectively.  

7: [2]D5 +24° > 0.5 (c = 0.5, CHCl3). IR, MS, and 1H-NMR spectrum are identical with those of 7.  

(+)-3-[2-(β-N-Ethoxycarbonyl-N-methylamino)ethyl]-4,5-methylenedioxybenzylidenyl]-6,7-dimethoxy-1(3H)-isobenzofuranone (12) and 3-[2-(β-N-Ethoxycarbonyl-N-methylamino)ethyl]-4,5-methylenedioxyphenyl]-6,7-dimethoxy-1(3H)-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).