

Optically Active Intermediate from the Degradation of (-)-Laudanosine, a Benzyloquinoline Alkaloid, with Ethyl Chloroformate

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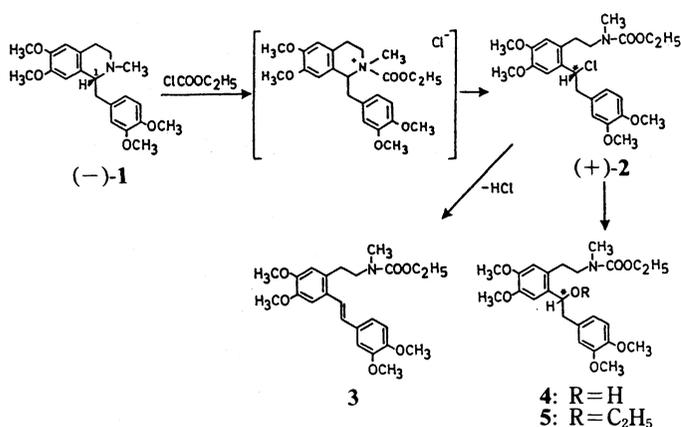
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Degradation of (-)-laudanosine, a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid, with ethyl chloroformate (ECF) afforded an optically active chloro-carbamate as an intermediate. The reason why this intermediate exhibits an optical activity was investigated by comparison with the reactions of some model compounds with ECF. It may be supposed that the chloride group in a hypothetical carbenium ion intermediate stands very closely to the chiral center, so conserving optical activity. However, a neighboring group effect can not be excluded.

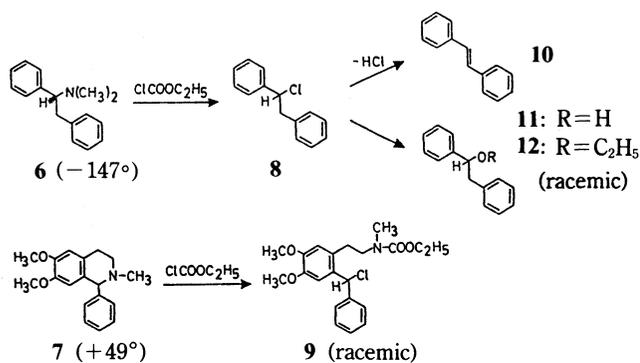
Introduction

Gadamer and Knoch¹ have reported that (-)-laudanosine

(1), a 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloid, was treated with ethyl chloroformate (ECF) and KOH in ether at room temperature to give a (+)-rotating organic phase,



Scheme 1



Scheme 2

probably of (+)-2, which liberated spontaneously HCl to afford the stilbene derivative 3 (Scheme 1). Therefore, they suggested 2 as an intermediate (Gadamer's intermediate) in this cleavage.

Recently, this experiment was repeated²; crude chloro-carbamate 2 was separated immediately by HPLC, indicating 80% of stilbene derivative 3 besides 18% of 2 and 2% of carbinol 4. Furthermore, an optically active ether 5 was isolated when 2 was purified by column chromatography using chloroform/ether 1:1, probably because of ethanol added to chloroform as a stabilizer. In another context we could isolate racemic 2 from racemic 1 under special reaction conditions and work-up techniques³.

In order to explain the optical activity of the intermediate 2 (Scheme 1) the following possibilities may be suggested. Primarily, it may be considered that the ethoxy-carbonyl group of the quaternary carbamate moiety can influence the benzylic C-atom, that is, a "neighboring group effect". Besides that, the kind of substituents at C-1 may also be important for this reaction. Therefore, we have synthesized two kinds of model compounds 6 and 7 (Scheme 2). In compound 6, which is a ring-opened model of laudanose(1), we intended to study a hypothetical neighboring group effect (cf. 13), because the benzylamine 6 is more flexible than the 1-benzyl-1,2,3,4-tetrahydroisoquinoline 1.

As already pointed out Gadamer's intermediate 2, a 1-chloro-1,2-diphenylethane-derivative, loses HCl leading to the pertinent stilbene. An analogous reaction would be impossible with the 1-phenyl-tetrahydroisoquinoline 7. We expected an enantiomer of 7 to be converted to an optically active, stable chloro-urethan, enabling us to determine its optical

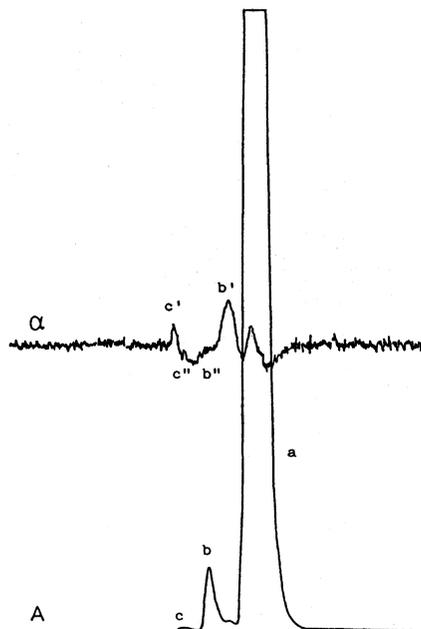


Figure 1. LC/UV/polarimeter-combination measurement of the reaction mixture of 6 with ethyl chloroformate [concentration: 1mg/ml, injection: 100 μ l, eluent: ethanol, temp.: 22°C, pressure: ~65 bar, UV (ERC 7210): 278 nm, polarimeter (PE 241): 365 nm]*.

purity and its absolute configuration.

Results and Discussion

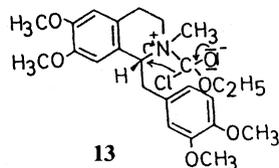
Racemic 1,2-diphenylethylamine was resolved⁴ and N-methylated⁵ by HCHO/HCOOH to give 6, and racemic 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline was resolved⁶ and N-methylated as described for 6 to afford 7. The optically active starting materials 6 and 7, respectively, were treated with ECF under reflux to yield the corresponding benzylchlorides 8 and 9 (Scheme 2). The optical activity ($[\alpha]_D = +3^\circ$) of 8 is very low in comparison with that of the starting material 6 ($[\alpha]_D = -147^\circ$). However, several instrumental data of 8 indicate that 8 is a crude product containing a small amount of *trans*-stilbene 10, although Hoeg *et al.*⁷ gave the elementary analysis for racemic 1,2-diphenylethylchloride (8) without further spectral data. In connection with this, the LC/UV/polarimeter-combination measurement (Figure 1) of the crude reaction mixture containing 8 and 10 besides N,N-dimethylcarbamate detected by ¹H-NMR spectroscopy as a side product was performed using a carbamate column.

The retention times of peak a, b and very small peak c from UV absorption in Figure 1 are 8.9, 7.2, and 6.4 respectively, which correspond to 10, 8 and 11 by comparison with those of authentic 10 and 11⁷. The c' + c'' obtained in the polarimeter track may correspond to the peak c, but we could not assign it definitively. The peaks b' + b'' correspond to the peak b for 8, the enantiomers b' and b'' reveal an approximate ratio of 1.7:1. However, this LC/UV/polarimeter-combination measurement can not be interpreted unequivocally. Because we do not know the optical purities of 2 and 8,

*We are thankful to Prof. Mannschreck, University of Regensburg, Germany, for this measurement.

we can not substantiate a neighboring group effect supposed for the formation of (+)-2 (Scheme 1). On the other hand, when 8 was hydrolyzed with water or etherified with ethanol, racemic 11 and 12 (Scheme 2) were obtained, respectively, whilst etherification of (+)-2 gave optically active ether 5. This difference points toward a neighboring group effect in that experiment. However, it should be realized that 6 lacks the OCH₃-groups stabilizing a hypothetical carbenium ion intermediate at the benzylic C-atom. Various attempts to prepare the tetramethoxy-substituted analogue of 6 led to a mixture of undesired products only.

Contrary to this, 9 shows no optical activity, this may result from the fact that the steric inhibition by the benzene ring bound directly at C-1 in 7 facilitates the racemization by shielding a (resonance stabilized) carbenium ion generated at C-1. Hence, it may be supposed from this experiment that in case of the chloro-carbamate (+)-2 the chloride in intermediate 13 can more closely approach toward the chiral center C-1. So its optical activity may be conserved. This is somewhat analogous to the reaction of R-O-SO-Cl leading to R-Cl+SO₂ and to the decomposition of R-O-CO-Cl in R-Cl+CO₂.¹¹



Experimental

Melting points were taken on Büchi SMP-20 apparatus, and are uncorrected. IR spectra were obtained on a Beckman Acculab III. ¹H-NMR spectra were recorded on a Bruker WH 90 (90 MHz) in CDCl₃ solution with TMS as an internal standard. UV spectra were measured using Uvikon 810 (Kontron). MS spectra were determined on a Varian MAT CH5 at 70 eV. Optical rotations were measured using Perkin Elmer 241 MC polarimeter. Microanalyses were performed on a Heraeus CHN-Rapid. TLC was done on Kieselgel 60F-254 aluminum plates (Merck). Column chromatography was done on Kieselgel 230 mesh (Merck). Ethyl chloroformate (ECF) was freshly distilled before use.

(-)-N,N-Dimethyl-1,2-diphenylethylamine (6)

Optical resolution of racemic 1,2-diphenylethylamine. 9.87 g (0.05 mol) (±)-1,2-diphenylethylamine was added under stirring to a hot solution of 7.5 g (0.05 mol) L (+)-tartaric acid in 50 ml hot water. After 10 min, white crystals in a still hot mixture were immediately filtered and recrystallized with dilute acetic acid to give the tartrate of a starting material: mp. 227-228°C (229-230°C)⁸. This diastereomeric salt was treated with 10% NaOH and extracted with ether. Removal of the solvent gave the (-)-base as an oily product. bp_{0.5} 127-128°C (bp_{0.35} 115-120°C)⁴, [α]_D²⁰ = -49.4° (c=0.5, EtOH; [α]_D¹⁹ = -51.2°⁸). IR: 3300 and 3380 cm⁻¹ (NH₂). HCl-salt: mp. 259-260°C (257-261°C)⁹, [α]_D²⁰ = -168.4° (C=0.5, H₂O; [α]_D²⁵ = -128°⁹). Anal. Calcd for C₁₄H₁₆ClN: C, 71.9; H, 6.91; N, 5.99. Found: C, 71.8; H, 6.91; N, 5.87.

Preparation of 6. 0.7 g Formic acid (99-100%) was slowly added under cooling to 0.6 g (3 mmol) of the above (-)-1,2-diphenylethylamine. 1.3 ml 37% formaldehyde was

added to this solution and the mixture was refluxed for 48 h. After removal of excess formaldehyde, the aqueous layer was basified and then extracted with ether. Removal of the solvent afforded an oily product which was purified by column chromatography with ether. [α]_D²⁰ = -147.0° (c=0.5, EtOH). ¹H-NMR δ (ppm): 2.23 (s; 6H, -N(CH₃)₂), 2.87-3.53 (ABX for -CH-CH₂; see reference⁵), 6.83-7.27 (m; 10H, aromatic). MS m/z (% relative intensity): 135(12), 134(100), 119 (8), 91(12), 77(7). 6·HCl: mp. 230-231°C (218-219°C)⁵. [α]_D²⁰ = -94.4° (c=0.5, H₂O; [α]_D²⁰ = -91.7°⁵).

(+)-6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (7)

Preparation of racemic 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline. Above material was prepared from homoveratrylamine using Pictet-Spengler cyclization as reported¹⁰. mp. 112-113°C (112-114°C)¹⁰. IR: 3320 cm⁻¹ (NH). ¹H-NMR δ (ppm): 1.93 (s; 1H, NH), 2.63-2.97 (m; 2H, -CH₂-), 3.00-3.27 (m; 2H, -CH₂-), 3.60 and 3.83 (2xs; 6H, -OCH₃), 5.03 (s; 1H, H-1), 6.23 and 6.60 (2xs; 2H, aromatic), 7.27 (s; 5H, phenyl).

Optical resolution of the above racemate. A mixture of 2.7 g (10 mmol) above racemate and 3 g (-)-diacetone-2-keto-1-gulonic acid hydrate⁶ was dissolved in hot isopropanol. Standing overnight yields the salt as colourless crystals. mp. 201-204°C, [α]_D²⁰ = -18° (c=0.5, H₂O). (-)-Base was liberated from above diastereomeric salt with 10% NaOH: colourless crystals, mp. 132°C. [α]_D²⁰ = -20 (c=0.5, CHCl₃). IR- and ¹H-NMR spectra are identical with those of the racemate.

Preparation of 7. 7 was prepared by the procedure described for 6 using formic acid and formaldehyde: mp. 85-86°C. [α]_D²⁰ = +49° (c=0.5, CHCl₃). ¹H-NMR δ (ppm): 2.17 (s; 3H, -NCH₃), 2.53-2.83 (m; 2H, -CH₂-), 2.97-3.27 (m, 2H, -CH₂-), 3.53 and 3.83 (2xs; 6H, -OCH₃), 4.20 (s; 1H, H-1), 6.10 and 6.60 (2xs; 2H, aromatic), 7.27 (s; 5H, phenyl).

1,2-Diphenylethylchloride (8)

1.13 g (5 mmol) 6 in 10 ml absolute CH₂Cl₂ were treated with excess ECF under reflux for 30 min. After cooling, the mixture was evaporated to give a crude oily product which was distilled *i. vac.* (distillation at atmospheric pressure causes extensive dehydrochlorination of 8)⁷. UV-, ¹H-NMR- and MS spectra indicate that this product contains a small amount of *trans*-stilbene (10). bp_{0.5} 121-123°C. [α]_D²⁰ = +3° (c=0.5, EtOH). UV (qualitative in MeOH) λ_{max}: 309 (sh), 294 (sh), 262, 226 nm. ¹H-NMR δ (ppm): 3.33 (d; J=7.5 Hz, 2H, -CH₂-), 5.03 (t; J=7.5 Hz, 1H, methine), 6.97-7.63 (aromatic protons from 8 and vinyl protons from 10). MS m/z (% relative intensity): 216 (M⁺, 46), 181(27), 180(26), 179(29), 178 (25), 165(18), 127(30), 125(89), 91(100), 89(16).

Trans-stilbene (10)

10 was separated from the mixture of 8 and 10 (see above) by preparative TLC with petroleum ether. Recrystallization with petroleum ether led to colourless needles. R_f=0.16 for 8 and 0.24 for 10. mp. 122-123°C (124°C)⁷. IR-, UV- (λ_{max}: 307, 292, 227, 204 nm) and ¹H-NMR [δ (ppm): 7.07 (s; 2H, vinyl), 7.17-7.60 (m; 10H, aromatic)] spectra are identical with authentic spectra⁷.

1,2-Diphenylethanol (11)

11 was obtained from 8 under reflux with water as reported⁷. Recrystallization of a crude product with petroleum ether gave colourless prisms which are optically inactive; mp. 65-

66°C (63.5-65°C)⁷. IR: 3320 cm⁻¹ (OH). UV (MeOH) λ_{max} (log ϵ): 217(3.73), 253(2.54), 258(2.63), 264 nm (2.52). ¹H-NMR δ (ppm): 1.97 (s; 1H, -OH), 2.85 (d; J=6.0 Hz, 2H, -CH₂-), 4.67 (t; J=6.0 Hz, methine), 6.90-7.33 (m; 10H, aromatic).

1-Ethoxy-1,2-diphenylethane (12)

12 was prepared from 8 with ethanol under reflux as described for 8 to 11. Purification by column chromatography with ether gave a colourless oil which shows no optical activity. ¹H-NMR δ (ppm): 1.03 (t; J=7.5 Hz, 3H, -CH₂-CH₃), 2.70 (d; J=7.5 Hz, 2H, -CH-CH₂-), 3.80 (q; J=7.5 Hz, 2H, -CH₂-CH₃), 4.27 (t; J=7.5 Hz, 1H, -CH-CH₂-), 7.00-7.60 (m; 10H, aromatic).

1-Chloro-1-[2-(β -N-ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-1-phenyl-methane (9)

0.14 g (0.5 mmol) 7 in 10 ml absolute CH₂Cl₂ were treated with excess ECF under reflux for 3 h. After cooling, the solvent and excess ECF were thoroughly removed *i. vac.*, the remained oily material was purified by column chromatography with CHCl₃/ether 1:1 to afford oily 9 which exhibits no optical activity. IR: 1700 cm⁻¹ (CO). ¹H-NMR δ (ppm): 1.16 (t; J=7.0 Hz, 3H, -CH₂-CH₃), 2.77 (s; 3H, -NCH₃), 2.40-3.67 (m; 4H, -CH₂-CH₂-), 3.73 and 3.83 (2xs; 6H, -OCH₃), 4.07 (q; J=7.0 Hz, 2H, -CH₂-CH₃), 6.07 (s; broad, 1H, H-1), 6.63 (s; 1H, H-6'), 6.90 (s; broad, 1H, H-3'), 7.30 (s; 5H, phenyl).

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