Determination of Optical Purity by Mass Spectrometry

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MS-Isotope Dilution Analysis (MS-IDA) with deuterated **2** as standard was used to determine the optical purity of crystalline (+)-**2**, obtained from optically pure (+)-**1** with ethyl chloroformate.

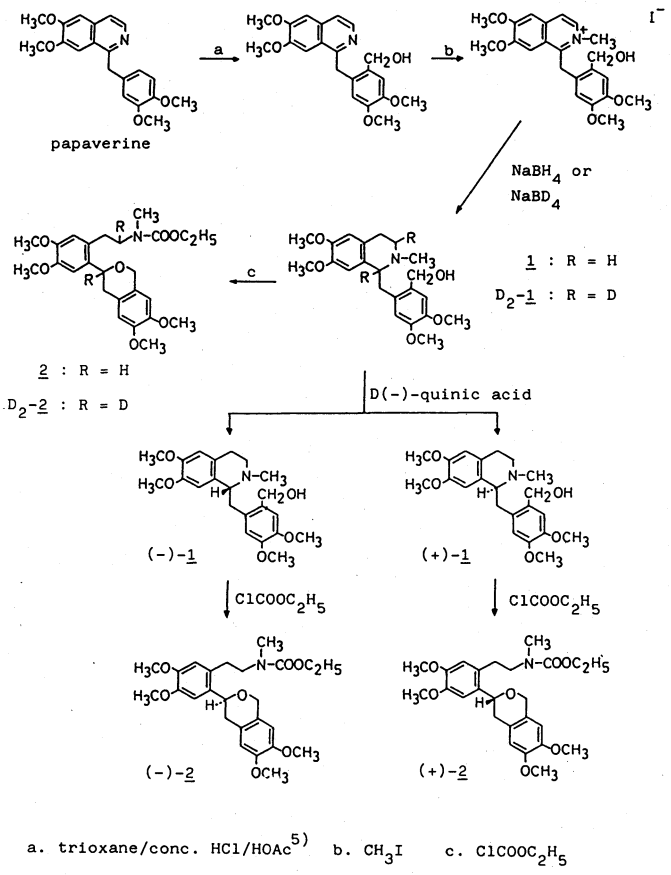
Bestimmung der optischen Reinheit durch Massenspektrometrie

Durch MS-Isotopenverdünnungsanalyse (MS-IDA) wurde die optische Reinheit von kristallinem (+)-**2** bestimmt, das aus optisch reinem (+)-**1** durch Chlorameisensäureethylester entsteht. Deuteriertes **2** diente als Standard.

1-(2-Hydroxymethylbenzyl)-N-methyl-1,2,3,4-tetrahydroisoquinolines, e. g. **1** are converted with ethyl chloroformate (ECF) to 3-phenylisochromans, e. g. **2**, (mainly) by an intramolecular S_N-reaction with inversion at C-1 of the tetrahydroisoquinoline moiety[1)]. In 1973[2)], however, we concluded that a carbenium ion might be an intermediate because optically pure **1**, when treated with ECF led to crystals of **2**, mp. 149–150 °C (authentic **2**-racemate: mp. 151 °C[2)]) showing an IR-spectrum (KBr) superimposible with that of racemic **2**. Even in high concentrations these *crystals* did not show any optical activity in their CD-spectrum, and their ORD-spectrum revealed only a slight deviation from the baseline. – Later we found that the *crude* product **2** shows optical activity, and the optical purity was determined by an isotope dilution method using ^{3}H-**2** to be 82 %[3)]. In addition, the crystals mentioned above do rotate plane-polarized light when high concentrations in another solvent ($CHCl_3$) and an increased length of light path through the solution were applied for polarimetric measurement[3)].

These results need an explanation. We repeated the conversion of (+)-**1** to (+)-**2**, separated the crystals, did not recrystallize them (m. p. 144 °C; $[\alpha]_D^{20} = +21°$) and determined their optical purity by mass spectrometric isotope dilution analysis (MS-IDA), using *Gerlach's* idea who determined the optical purity of benzylamines[4)].

The preparation of the compounds used in these experiments is shown and explained in Scheme 1.



In quantitative ms-analysis the overall error for the determination results from the cumulative effect of the errors introduced by different parts of the system[6)]. Therefore, we constructed calibration curves covering the range of samples likely to be encountered for quantitative determination. Mixtures of unlabeled and labeled racemic isochromans **2** and D_2-**2** were primarily measured at 70 and 12 eV, respectively. To this end **2** and D_2-**2** were mixed in nine different molar ratios (table 1), each mixture was recrystallized four times from isopropanol and measured at least 30 × at 70 and 12 eV. Peak intensities of the averages were calculated and corrected for the ^{13}C satellite, in order to avoid difficulties

Tab. 1: Mixtures of (±)-**2** and (±)-D_2-**2**

Sample	(±)-2	(±)-D_2-2	Sample	(±)-2	(±)-D_2-2
1	0.0501 mmol	0.0502 mmol	6	0.0406 mmol	0.0605 mmol
2	0.0605 mmol	0.0413 mmol	7	0.0304 mmol	0.0704 mmol
3	0.0706 mmol	0.0307 mmol	8	0.0200 mmol	0.0806 mmol
4	0.0805 mmol	0.0207 mmol	9	0.0103 mmol	0.0900 mmol
5	0.0901 mmol	0.0101 mmol			

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which may arise with multiply labeled compounds (^2H plus ^{13}C; average abundance 0.015 and 1.11 % for ^2H and ^{13}C, respectively). Therefore, the contribution of ^{13}C containing ions to m/z 459 ($M^{+\cdot}$ of **2**) has been substracted according to *Seibl*[7]:

$$I\,(M+2) = \frac{(1.1 \cdot n)^2}{200} = 3.8\,\%\,IM$$

IM = Intensity of m/z 459 (**2**)
n = 25 (**2** contains 25 C-atoms)

In sample 1 (table 1), for instance, m/z 459 and m/z 461 show 161.0 mm and 165.9 mm as average peak height. Thus, the corrected intensity for m/z 461 corresponds to
[165.9–(161.0 · 0.038)] = 159.8 mm, and therefore, the isotope ratio to

$$I\,\frac{d_2}{d_o} = \frac{159.8}{161.0} = 0.993 \text{ (Table 2)}$$

The values of Table 2 afford the calibration curves (Fig. 1), which prove that D_2-**2** can be used as an internal standard[6].

Tab. 2: Calculated data of molar ratio and isotope ratio for mixtures of labeled and unlabeled standards **(2)** 1–9 (70/12 eV)

Sample	Mol $\frac{d_2}{d_o}$	I $\frac{d_2}{d_o}$ (70 eV)	I $\frac{d_2}{d_o}$ (12 eV)
1	1.002	1.038	0.993
2	0.683	0.725	0.687
3	0.435	0.483	0.445
4	0.257	0.312	0.275
5	0.112	0.163	0.127
6	1.490	1.517	1.471
7	2.316	2.297	2.246
8	4.030	3.889	3.841
9	8.738	8.143	8.375

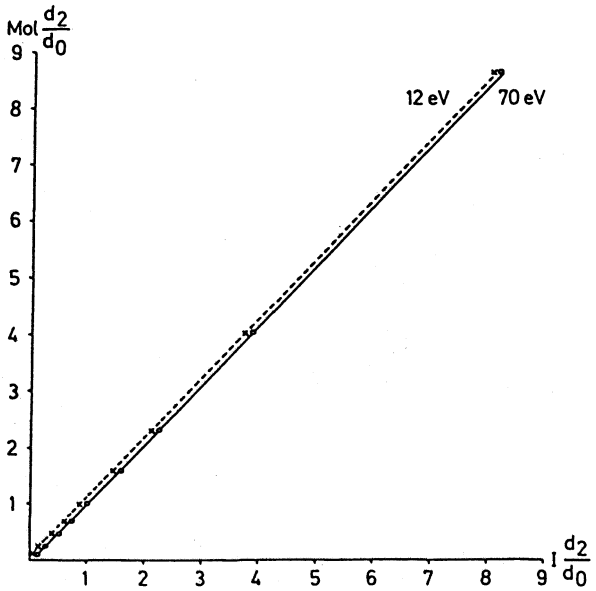

Fig. 1: Calibration curves

To determine the optical purity of the crystals of (+)-**2** ($[\alpha]_D^{20} = +21°$) 0.0506 mmol of (+)-**2** and 0.0505 mmol of (racemic) labeled isomer D_2-**2** were mixed and recrystallized four times from isopropanol until no more optical activity is shown. This mixture of racemates was measured as indicated for the samples 1–9 to obtain the values 1.014 (70 eV) and 1.015 (12 eV) for the isotope ratio I d_2/d_o. The optical purity was calculated using Berson's equation[8] which had also been used in lit.[3].

$$E = [(X + B)^2 - (C_O/C)\cdot(X^2 + BX)]^{1/2}$$

$$\%\text{ optical purity} = E \cdot 100/B$$

B: weight of the test sample ((+)-**2**)
E: excess of one enantiomer in B
X: weight of the labeled racemate added to the test sample (D_2-**2**)
C_o: specific activity*) of the labeled racemate added to the test sample
C: specific activity*) of the reisolated racemate.

B = 23.26 mg; X = 23.33 mg; C_o = 100 % d_2;
C = I d_2/d_o = 1.015 (or 1.014) = 50.4 % d_2,
therefore, E = 4.30 and the optical purity = 18.5 %.

Obviously in this case the racemate (racemic mixture) of **2** is enriched by crystallization.

*) Instead of the specific (radio)activity we used the D-content.

Experimental Part

Mp.: uncorrected, Büchi SMP-20. – *Elementary analysis:* Microanalytical Laboratory of the Univ. of Regensburg. – *IR* (KBr): Beckman Acculab III. – ^{1}*H-NMR:* Varian EM 390 (90 MHz), 30 °C, TMS int. stand. – *UV*: Uvikon 810, MeOH (Uvasol „Merck"). – *MS*: Varian MAT CH5 and 311 A.

6'-Hydroxymethylpapaverine: lit.[5]

6'-Hydroxymethylpapaverine-N-methyliodide: lit.[2]

6'-Hydroxymethyllaudanosine **(1)**

15.3 g (0.03 mol) 6'-hydroxymethylpapaverine-N-methyliodide dissolved in 900 ml 70 % EtOH were added dropwise to a stirred suspension of 5.0 g (0.12 mol) $NaBH_4$ in 90 ml 70 % EtOH at 0 °C. After refluxing for 4 h, the org. layer was evaporated and the remaining aqueous layer was extracted with $CHCl_3$. Drying and removal of the solvent led to an oily product, colourless needles from Et_2O: 6.4 g (55 %), mp. 99–100 °C (103–104 °C[2]). – ^{1}H-NMR: δ (ppm) = 2.17–3.23 (m; 7H, -CH_2- and H-1), 2.3 (s; 3H, -NCH_3), 3.63 (s; 3H, -OCH_3), 3.83 (s; 6H, -OCH_3), 3.88 (s; 3H, -OCH_3), 4.43 (s; 2H, -$C\underline{H}_2$OH), 6.27, 6.50, 6.70 and 6.83 (4 × s; 4H, aromatic).

(±)-3-[2'-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4',5'-dimethoxyphenyl]-6,7-dimethoxyisochroman **((±)-2).**

(±)-**1** was reacted with ECF as reported[2] to give (±)-**2**, mp. 147–148 °C (150–151 °C[2]). – IR: 1700 cm^{-1} (CO). – UV: λ max (log ε) = 282 (3.99), 231 (4.32), 208 nm (4.75). – ^{1}H-NMR: δ (ppm) = 1.17 (t; J = 6 Hz, 3 H, -CH_2-CH_3), 2.73–3.63 (m; 7H, -CH_2- and H-3), 3.87 (s; 12H, -OCH_3), 4.07 (q; J = 6 Hz, 2H, -$C\underline{H}_2$-CH_3), 4.90 (s; 2H, -O-CH_2-), 6.53, 6.63, 6.67 and 7.07 (4 × s; 4H, aromatic).

Enantiomers of **1**

(±)-**1** was resolved with D-(–)-quinic acid[2] to give its enantiomers.
(+)-**1**: mp. 125 °C (125 °C[2]), $[\alpha]_D^{20} = +88°$ (c = 3.0, $CHCl_3$).
(–)-**1**: mp. 126 °C (124 °C[2]), $[\alpha]_D^{20} = -88°$ (c = 3.0, $CHCl_3$).

Enantiomers of **2**

The enantiomers of **2** were prepared from (+)-**1** and (–)-**1** with ECF as reported[1, 2].

(±)-1,3-Dideutero-6'-hydroxymethyllaudanosine ((±)-D_2-**1**)

(±)-D_2-**1** was prepared from 6'-hydroxymethylpapaverine-N-methyliodide with $NaBD_4$ as described for **1**; mp. 99 °C.
$C_{22}H_{27}D_2NO_5$ (389.5) calcd. C 67.8 H 7.03 found C 67.8 H 7.00. – IR: 3150 cm^{-1} (OH). – UV: λ max (log ε) = 283 (3.84), 212 nm (4.42). – ^{1}H-NMR: δ (ppm) = 2.30 (s; 3H, $-NCH_3$), 2.13–3.30 (m; 5H), 3.67 3.83, 3.85 and 3.90 (4 × s; 12H, $-OCH_3$), 4.43 (s; 2H, $-C\underline{H}_2OH$), 6.27, 6.50, 6.67 and 6.80 (4 × s; 4H, aromatic). – MS (70eV): m/z = 209 (15 %), 208 (100), 193 (5), 192 (9).

(±)-3-Deutero-3-[2'-(β-deutero-β-N-ethoxycarbonyl-N-methylamino-ethyl)-4',5'-dimethoxyphenyl)]-6,7-dimethoxyisochroman ((±)-D_2-**2**).

(±)-D_2-**2** was prepared from (±)-D_2-**1** with ECF as reported for undeuterated (±)-**2**[2]; mp. 145°–146 °C.

$C_{25}H_{31}D_2NO_7$ (461.5) calcd. C 65.0 H 6.78 found C 65.1 H 6.78. – IR: 1710 cm^{-1} (CO). – UV: λ max (log ε) = 282 (3.92), 230 (4.28), 212 nm (4.40). – ^{1}H-NMR: δ (ppm) = 1.50 (s; broad, 3H, $-CH_2-C\underline{H}_3$), 2.63–3.87 (m; 5H, $-CH_2-$ and -CH-D-), 3.87 (s; 12H, $-OCH_3$), 4.03 (q; J = 6 Hz, 2H, $-C\underline{H}_2-CH_3$), 6.57, 6.63, 6.67 and 7.07 (4 × s; 4H, aromatic). – MS (70 eV): m/z = 461 ($M^{+\cdot}$, 7 %), 443 (1, * 425.70), 358 (5), 340 (5), 180 (5), 165 (14), 164 (100), 149 (7, *135.37), 117 (7).

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