Mild Reductive Cleavage of α-Aminoethers

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1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisoquinoline (1) is converted by ethyl chloroformate (ECF)/NaBH₃CN to 2-[β-(N-ethoxycarbonyl-N-methyl)aminoethyl]-4,5-dimethoxytoluene (4) via the quaternary urethane 2. The same procedure leads from laudanosine (5) to the dibenzyl derivative

**) Dedicated with kind regards to Prof. Dr. Dr. h.c. H.H. Inhoffen on the occasion of his 80th anniversary.
9. The reaction with ECF/NaBH₃CN followed by LiAlH₄ reduction is a versatile approach to Emde degradation products avoiding strongly basic conditions and elevated temperature. Cleavage reactions of other α-amino ethers, e.g. thebaine (18), and N-demethylation reactions of the tetrahydroisoquinolines 1 and 10 with ECF are reported.

Reduzierende α-Aminoether-Spaltung unter milden Bedingungen


C-1-N bond cleavage of the tetrahydroisoquinoline system has been accomplished by various methods, e.g. Hofmann-degradation, Pt-catalyzed hydrogenation or reductive cleavage with Na-amalgam after quaternization (Emde-degradation)³, using cyanogen bromide and ethylchloroformate (ECF), introduced into the chemistry of N-alkylated 1,2,3,4-tetrahydroisoquinolines by Gadamer. This paper is concerned with a modified ECF-method. Recently Calverley has described a reductive benzylamine cleavage of the carboline ring system with ECF in absol. THF at -70 °C followed by NaBH₃CN at room temp. He discusses the participation of H⁻ as a nucleophile. This can be interpreted as a SN₁-reaction of H⁻ at the benzylic C-atom of a quaternary urethane.

Benzylchlorides have been reduced to toluenes using NaBH₃CN. This leads to the suggestion that nucleophilic attack of Cl⁻ at the benzylic C-Atom at room temp. converts a quaternary urethane (e.g. 2a) into a o-chloromethyl-substituted tertiary urethane (e.g. 3a) which in turn is reduced to a toluene (e.g. 4). These alternatives are outlined in scheme 1.

Quaternary urethanes of type 2a are known to be very sensitive to temp. and to moisture, but they can be isolated under special conditions. When 1,2,3,4-tetrahydro-6,7-dimethoxy-N-methylisoquinoline (1) was treated with freshly distilled ECF at -70 °C,
the quaternary urethane 2a was obtained. It was identified by its IR-spectrum taken at low temp. the spectrum exhibits a characteristic CO-band at 1820 cm\(^{-1}\) which disappeared gradually when the pellet was allowed to warm up to room temp.; at the same rate a new CO-band at 1700 cm\(^{-1}\) (R-N(CH\(_3\))-COOEt) arose. The new spectrum was identical with that of 3a, obtained by prolonged refluxing 1 with a large excess of ECF. 3a is converted to 4 by NaBH\(_3\)CN at room temp. and to 3b by water.

LiAlH\(_4\) reduces the benzylchloride- and the urethane- moiety in 3a leading to 2-(β-dimethylaminoethyl)-4,5-dimethoxytoluene, isolated as its HCl-salt (mp. 195°).

As already mentioned, Calverley\(^6\) assumes nucleophilic attack of H\(^\ominus\) which in our case would mean a direct conversion of 2a into 4. At -70 °C, however, 2a was not converted into 4 by NaBH\(_3\)CN. In order to prove a direct conversion 2 to 4 at room temp., we have prepared the more stable intermediate 2b by reacting 2a with silvertetrafluoroborate in THF at low temp. 2b was stable at least for 4 d at room temp. 2b was treated with NaBH\(_3\)CN at room temp. to give 4. This experiment supports Calverley's statement, but does not rule out tertiary urethanes, e.g. 3a, as intermediates, as long as good nucleophiles act as counterions of the quaternary urethanes, e.g. 2a. – Surprisingly, 2a and 2b are converted to the starting material 1 by NH\(_4\)OH.
When Gadamer and Knoch\footnote{When Gadamer and Knoch\textsuperscript{5} treated \((-\)-)laudanosine with ECF/KOH in ether at room temp. they obtained a \((+)-\)rotating organic phase which liberated HCl to the stilbene 8. We studied the conversion of \((+/-)-5\) to 9 (scheme 2) and isolated 7a, the racemate of an intermediate, postulated by Gadamer\textsuperscript{5}). We got a faint hint for a further intermediate \((6?)\) from nmr-tube experiments, but up to now we could not trap it. When 5 was treated with ECF at \(-70^\circ\) in the presence of \(	extrm{AgBF}_4\) (compare 2\textsuperscript{a} \textrightarrow 2\textsuperscript{b}), a double salt 5\textsuperscript{2} \cdot \textrm{AgBF}_4 was isolated. Treatment of 5 with ECF at \(-70^\circ\) for 30 min. followed by addition of cold \(	extrm{AgBF}_4\) in THF and work-up at room temp. led to stilbene 8. 7a was hydrolyzed to 7b, 7a splits off HCl to 8\textsuperscript{5}), which in turn is hydrogenated to 9. \(-5\) is also converted to 9 in a one-pot reaction (scheme 2). As urethane-like 4 and 9 are smoothly reduced by \(	extrm{LiAlH}_4\) to \(N,N\)-dimethylamines\textsuperscript{9}), the overall reactions 1 \textrightarrow 4 and 5 \textrightarrow 9 are mild alternatives to the Emde-degradation\textsuperscript{3}) which needs strong alkali at elevated temp. 1 and 5 are phenylogous \(\alpha\)-aminoethers. The unsubstituted tetrahydroisoquinoline 10, however, is reported not to react with ECF/OH\textsuperscript{0\textregistered}) and, contrary to 1, no C-1-N bond cleavage is observed with ECF/NaBH\textsubscript{3}CN. We got the cyanoborane adduct 11, normally obtained from tert. amines and NaBH\textsubscript{3}CN in THF\textsuperscript{11}) (scheme 3).

\[\begin{array}{c}
\text{N} \text{CH}_3 \\
\text{10}
\end{array}\]

\[\begin{array}{c}
\text{1. ECF} / \text{-70°} \\
\text{2. NaBH}_3CN/\text{RT} \\
\rightarrow \\
\text{11}
\end{array}\]

\[\begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
\text{12}
\end{array}\]

\[\begin{array}{c}
\text{1. ECF} \\
\text{2. NaBH}_3CN \\
\rightarrow \\
\text{13}
\end{array}\]

\[\begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3
\end{array}\]

\text{Scheme 3}

Knabe and Shukla\textsuperscript{12}) have studied the influence of electronic and steric effects on the benzylamine cleavage with ECF: their results correlate very well with our findings. The different behaviour of 1 and 10 might be explained by the \(+\text{M}\)-effect of the methoxygroups of 1 which could stabilize a transition state with a positively charged benzyllic C-atom. In addition, this ring cleavage is influenced by steric factors: Tetrahydroberberine (12) is not split to a hexahydro-dibenzo[c,g]azecine, but converted to its cyanoborane 13. 12 is regenerated from 13 by KOH.

Our results with phenylogous \(\alpha\)-aminoethers inaugurated experiments with the \(\alpha\)-aminoethers 14 and 16, respectively\textsuperscript{*}). 14 was converted to the ketoester 15 by ECF/KOH, probably via quaternization, formal nucleophilic substitution by OH\textsuperscript{0} and

\textsuperscript{*} We are thankful to Prof. Eiden, München, for intensive discussions and for providing compound 14 (F. Eiden, W. Winkler, K.Th. Wanner and A. Markhauser, Arch. Pharm. 318, 648 (1985).)
successive tautomerization. On the other hand, 14 was only reduced with ECF/NaBH$_3$CN or NaBH$_3$CN to its dihydro-derivative 16, which was, however, cleaved with ECF/KOH to the ester 17 (Scheme 4).

According to Eiden, the stereochemistry of 14 is not known. However, the conversion of dihydro-14 (16) to 17 points towards a cis-annelation in the hexahydrochroman-system 16 and in the hexahydrochromene 14.

Phenyllogous $\alpha$-aminoethers are expected to resemble their vinylogous analogues. When thebaine (18), a twofold vinylogous $\alpha$-aminoether, was treated with ECF in boiling toluene, thebaol (20) arose as the main product, whilst at 0° 19 was dominant. 19 was separated from 20 by tlc, but elution from the sorption layer afforded again a mixture of 19 and 20. Therefore, we consider 19 to be an intermediate between 18 and 20. Vieböck et
al.\textsuperscript{13} have treated 18 with ECF and various acid anhydrides. With ECF they obtained 21. The formation of 21 from 18 points towards a cleavage of a twofold vinylogous α-aminoether, whilst 19 looks like a product of β-elimination. Vieböck et al.\textsuperscript{13} have got the quaternary oxazolinium salt 22 when treating 18 with benzoylchloride. This offers an explanation for the conversion 19 to 20, which is outlined in scheme 5.

The cleavage of the benzyl-nitrogen bond reported in this paper has been accomplished by excess ECF. N-Demethylation by ECF is a well known procedure\textsuperscript{14}, especially, if the N-CH\textsubscript{3} group does not belong to a benzylamine moiety. So we tried to find proper conditions for N-demethylation without cleaving the C-1-N bond in 1,2,3,4-tetrahydro-N-methylisoquinolines. When 1 and 10 were reacted with one mol equiv. of ECF, the N-demethylated urethanes 23 and 24 were obtained in fair yields. 2a was found to be an intermediate in the conversion of 1 to 23. The urethane 25 was obtained by using Cl-CO-OCH\textsubscript{2}CCl\textsubscript{3} instead of ECF. 25 is easily reduced by Zn/acetic acid\textsuperscript{15} to 26, which is then converted to 23 by ECF (Scheme 6).

![Scheme 6](image)

**Experimental Section**

*MP: Büchi SMP-20 apparatus, uncorr. Elementary Analysis: Microanalysis Laboratory of University Regensburg. IR Spectra: Beckman Acculab III. - ¹H-NMR Spectra: Bruker WH 90 (90 MHz) and Bruker Spectrospin (250 MHz) in CDC\textsubscript{3}, TMS int. stand. - MS: Varian MAT CH 5. - UV Spectra: Uvikon 810 (Kontron). - Ethylchloroformate was freshly distilled before use. - Column chromatography: Kieselgel (230 mesh, Merck), CHCl\textsubscript{3}/ether 1:1 as eluent. - All reactions were performed under N\textsubscript{2}.*

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium-salts: chloride (2a), tetrafluoroborate (2b)

**2a:** 0.21 g (1 mmol) in 5 ml absol. CH\textsubscript{2}Cl\textsubscript{2} were treated with 0.1 ml (1 mmol) ECF for 30 min at −70°. After evaporation at −30°, the IR spectrum of the residue was run in a cold paraffin mull\textsuperscript{8}. CO-band at 1820 cm\textsuperscript{-1}.

**2b:** 0.1 g (0.5 mmol) 1 in 5 ml absol. THF were reacted with 0.05 ml (0.5 mmol) ECF at −70°. 30 min later, 0.1 g AgBF\textsubscript{4} was added and stirred for 30 min at −70°. The solid (mixture of 2b and AgCl) was washed with THF. IR: 1820 cm\textsuperscript{-1} (CO). - ¹H-NMR: δ(ppm) = 1.27 (t; J = 7 Hz, 3H, -CH\textsubscript{2}-CH\textsubscript{3}), 2.87–3.27 (m; 4H, -CH\textsubscript{2}-CH\textsubscript{2}-N-), 3.47 (s; 2H, -CH\textsubscript{2}-N-), 3.73 (s; 3H, -NCH\textsubscript{3}), 3.77 and 3.80 (2 x s; 6H, -OCH\textsubscript{3}), 4.50 (q; J = 7 Hz, 2H, -CH\textsubscript{2}-CH\textsubscript{3}), 6.67 (s; 2H, aromat.).

2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxybenzylchloride (3a)

0.62 g (3 mmol) in 10 ml absol. CH\textsubscript{2}Cl\textsubscript{2} and 5.7 ml (60 mmol) ECF were refluxed for 48 h. Removal of the solvent led to 0.95 g crude 3a. IR: 1700 cm\textsuperscript{-1} (CO). - ¹H-NMR: δ(ppm) = 1.23 (t; J =
2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxybenzylalcohol (3b)

0.4 g 3a in 5 ml acetone were reacted with 1 ml water for 4 h at room temp. The mixture was extracted with ether, concentration afforded 3b as an oil, which was purified chromatographically. IR: 3420 (OH), 1690 cm⁻¹ (CO).

-¹H-NMR: δ(ppm) = 1.20 (t; J = 7 Hz, 3H, -CH₂-CH₃), 2.70-3.67 (m; 4H, -CH₂-CH₂-), 2.85 (s; 3H, -NCH₃), 3.83 (s; 6H, -OCH₃), 4.05 (q; J = 7 Hz, 2H, -CH₂-CH₃), 4.60 (s; 2H, -CH₂C₁), 6.62 and 6.87 (2 x s; 2H, aromat.).

2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxytoluene (4)

0.31 g (1.5 mmol) 1 and 0.6 ml (6 mmol) ECF in 15 ml absol. THF were stirred at -70° for 1 h. Then dropwise addition of 0.19 g (3 mmol) NaBH₃CN in 45 ml absol. THF led to a crude material; column chromatography yielded a colourless oil: 0.31 g (74 %). IR: 1705 cm⁻¹ (CO). IDX-NMR: δ(ppm) = 1.23 (t; J = 7 Hz, 3H, -CH₂-CH₃), 2.50-3.57 (m; 6H, -CH₂-), 2.83 (s; 3H, -NCH₃), 3.80 (s; 3H, -OCH₃), 3.88 (s; 3H, -OCH₃), 3.92 (s; 3H, -OCH₃), 3.93 (s; 3H, -OCH₃), 5.35 (s; 18H, -OCH₃), 5.97 (s; 2H, aromat.), 6.40-6.67 (m; 8H, aromat.).

- MS-FD: m/z = 465 (M⁺), 429 (M⁺-HCl).

4 from 3a

0.2 g NaBH₃CN in 40 ml absol. THF were added to a stirred solution of 0.4 g 3a (see above) in 5 ml absol. THF. Stirring overnight at room temp. and usual work-up yielded 0.35 g 4. Physical data: 4 from 1.

Bis(laudanosine)-silver(I) tetrafluoroborate (5a)

0.18 g (0.5 mmol) 5 in 2 ml absol. CH₂Cl₂ and an excess AgBF₄ in 3 ml absol. THF were stirred with 0.05 ml (0.5 mmol) ECF for 30 min at -70°. After evaporation at room temp., a dark oily residue was obtained, which was dissolved in hot THF and precipitated after cooling: grey solid, mp. 216-219°. C₄₂H₅₄N₂₅0ₙAgBF₄ (909.7): calc. C 55.4 H 6.00 N 3.08 found C 54.9 H 6.22 N 3.08. IR: 1040-1130 cm⁻¹ (BF₄⁻). -I¹H-NMR (CF₃COOD): δ(ppm) = 2.53-3.27 (m; 14H), 3.33 (s; 6H, -NCH₃), 3.47 (s; 6H, -OCH₃), 3.53 (s; 18H, -OCH₃), 5.97 (s; 2H, aromat.), 6.40-6.67 (m; 8H, aromat.).

1-Chloro-1-[2-(β-N-ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)-ethane (7a)

0.71 g (2 mmol) (±)-laudanosine (5) were treated with 0.6 ml ECF without solvent for 30 min at -70°. Excess ECF was removed i. vac. at -30°: colourless oil. IR: 1690 cm⁻¹ (CO). – UV (absol. CHC₁₃) λ max (qual.): 246, 283 nm. – ¹H-NMR: δ(ppm) = 1.23 (t; J = 7 Hz, 3H, -CH₂-CH₃), 2.50-3.57 (m; 6H, -CH₂-), 2.83 (s; 3H, -NCH₃), 3.80 (s; 3H, -OCH₃), 3.88 (s; 3H, -OCH₃), 3.92 (s; 3H, -OCH₃), 3.98 (s; 3H, -OCH₃), 4.17 (q; J = 7 Hz, 2H, -CH₂-CH₃), 5.47 (t; J = 7.5 Hz, 1H, -CH-Cl), 6.48, 6.68, 6.75 and 6.78 (4 × s; 5H, aromat.) – MS-FD: m/z = 465 (M⁺), 429 (M⁺-HCl).

1-Hydroxy-1-[2-(β-N-ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)-ethane (7b)

0.1 g 7a in 5 ml cold acetone were stirred with 10 ml water for 2 h at room temp. 7b was separated from the mixture of 7b and 8 by column chromatography: mp. 110° (112°17)}.
from 5: 0.36 g (1 mmol) 5 in 10 ml absol. THF were stirred with 0.4 ml (4 mmol) ECF for 1 h at -70°.
The THF were added dropwise at -70° and the mixture was allowed to react overnight at room temp.
The mixture was diluted with water, basified with 0.1 N-NaOH and extracted with ether.
Removal of the solvent gave 9 as a colourless amorphous solid: 0.27 g (64%), mp. 124-125° (ether).
C_{24}H_{33}N_{6}O_{6} (431.6): calc. C 66.8 H 7.72 found C 67.2 H 7.81. IR: 1690 cm^{-1} (CO).
UV (MeOH) λ max (log e): 207 (4.50), 227 (4.27), 279 nm (3.85). - ^1H-NMR: δ(ppm) = 1.20 (t; J = 7 Hz, 3H, -CH\textsubscript{2}-CH\textsubscript{3}), 2.60-3.53 (m; 4H, -CH\textsubscript{2}-CH\textsubscript{2}-N-), 2.83 (s; 7H, -NCH\textsubscript{3}, -CH\textsubscript{2}-CH\textsubscript{2}-Ar.), 3.79 (s; 3H, -OCH\textsubscript{3}), 3.81 (s; 3H, -OCH\textsubscript{3}), 3.83 (s; 6H, -OCH\textsubscript{3}), 4.10 (q; J = 7 Hz, 2H, -CH\textsubscript{-CH\textsubscript{3}}), 6.60, 6.63, 6.72 and 6.75 (4 x s; 5H, aromat.).

from 8: 0.43 g (1 mmol) 8 in 30 ml CHCl\textsubscript{3} were hydrogenated with 0.3 g 10% Pd/C at room temp,
for 2h. 64% 9.

1,2,3,4-Tetrahydro-2-methylisoquinoline-cyanoborane (11) was obtained as a colourless amorphous solid by
reacting 0.29 g (2 mmol) 10 in 5 ml absol. THF with 0.8 ml (8 mmol) ECF at -70°, then adding 0.26 g (4 mmol)
NaBH\textsubscript{3}CN in 50 ml absol. THF. For working-up see 5 to 9: 0.25 g (67%), mp. 97° (ether). C_{10}H_{13}N_{2}BH\textsubscript{2}CN (186.1): calc. C 71.0 H 8.14
found C 70.9 H 8.21. - IR: 2400 (BH), 2260 cm^{-1} (CN). - ^1H-NMR: δ(ppm) = 2.70 (s; 3H, -NCH\textsubscript{3}), 2.83-3.43 (m; 4H, -CH\textsubscript{2}-CH\textsubscript{2}-), 3.90 and 4.30 (AB; J = 15 Hz, 2H, -CH\textsubscript{2}-), 6.90-7.27 (m; 4H, aromat.). - MS (-10 eV): m/z = 186 M\textsuperscript{+} (13 %), 185 (17 %), 184 (14 %), 183 (4 %), 159 (100 %), 158 (27%), 147 (42 %), 146 (20 %), 131 (9 %), 105 (17 %), 104 (16 %).

Tetrahydroberberine-cyanoborane (13) from 13 in a mixture of methanol/20% KOH (2:1) for 2 h yields 12.
mp. 168° (167°)).

α-Keto-γ-phenyl-γ-(2'-oxocyclohexenyl)-methylbutyrate (15)
0.36 g (1 mmol) 14 in 10 ml CH\textsubscript{2}Cl\textsubscript{2} were refluxed with 0.4 ml (4 mmol) ECF and 4 ml 15 % KOH for 4 h.
The organic residue was purified by column chromatography: 0.14 g (50 %) colourless solid. mp.
144°, C\textsubscript{17}H\textsubscript{20}O\textsubscript{4} (288.4): calc. C 70.8 H 7.00 found C 70.6 H 7.33. - IR: 3340 (OH), 1740 (CO), 1710 cm^{-1} (CO). - UV (MeOH) λ max (log e): 212 (4.21), 228 (sh), 286 nm (3.65). - ^1H-NMR: δ(ppm) = 1.57-3.74 (m; 12 H), 3.80 (s; 3H, COOCH\textsubscript{3}), 7.12-7.33 (m; 5H, -C\textsubscript{6}H\textsubscript{5}). - MS (70 eV): m/z = 288 (M\textsuperscript{+}, 37 %), 270 (9 %, *253.13), 229 (100 %, *182.09), 211 (15 %, *194.41), 191 (22 %), 131 (69 %, *74.94), 125 (35 %), 97 (48 %), 91 (39 %). - The corresponding 1-ethoxycarbonylpiperidine 15a was
detected by its IR spectrum (1700 cm^{-1}, CO) and by tlc in comparison with an authentic sample21.
2,3,4a,5,6,7,8,8a-Octahydro-2-methoxycarbonyl-4-phenyl-8a-piperidino-4H-chromene (16)

0.18 g (0.5 mmol) 14 in 5 ml absol. CH₂Cl₂ were reacted with 0.2 ml (2 mmol) ECF for 1 h at -70°, then 0.1 g NaBH₃CN in 20 ml absol. THF were added dropwise. The mixture was stirred overnight at room temp. and worked up as described for 5 to 9. The oily residue was purified by column chromatography: colourless solid, 0.12 g (70%), mp. 143°. - IR: 1730 cm⁻¹ (CO). - ¹H-NMR: δ(ppm) = 0.93-3.43 (m; 23 H), 3.77 (s; 3H, -COOCH₃), 7.03-7.70 (m; 5H, -C₆H₅). - MS (70 eV): m/z = 357 (M⁺⁺, 12 %), 341 (26 %), 340 (100 %), 299 (11 %), 298 (48 %), 226 (5 %), 212 (7 %), 197 (11 %), 194 (16 %).

α-Ethoxycarbonyloxy-γ-phenyl-γ-(2'-piperidino-1'-cyclohexen(V)-yl)-methylbutyrate (17)

A mixture of 0.07 g (0.2 mmol) 16 in 5 ml absol. CH₂Cl₂, 0.1 ml (1 mmol) ECF and 3 ml 15 % KOH was stirred under reflux for 6 h. After usual work-up, the oily residue was purified by column chromatography (Kieselgel, ethylacetate): colourless oil. IR: 1750 cm⁻¹ (CO). - UV (MeOH) X max (qual.): 202, 250-270 nm (sh). - ¹H-NMR (250 MHz): δ(ppm) = 1.30 (t; J = 6.9 Hz, 3H, -CH₂-CH₃), 1.35-3.00 (m; 22H), 3.77 (s; -OCH₃), 4.16 (q; J = 6.9 Hz, 2H, -CH₂-CH₃), 7.11-7.28 (m; 5H, -C₆H₅). - MS (70 eV): m/z = 370 (3 %), 341 (27 %), 340 (100 %), 281 (11 %), 270 (9 %), 149 (23 %), 124 (20 %). - MS-FD: m/z = 429 (M⁺#).

Thebaol (20)

0.31 g (1 mmol) thebaine (18) in 15 ml absol. toluene were refluxed with 0.1 ml (1 mmol) ECF for 2 h. 20 was separated from the cone, residue with column chromatography (Kieselgel, CHCl₃): yellow solid: 0.14 g (55 %), mp. 93-94°; (92.5-93.5 °C). C₁₆H₁₄NO₃ (254.3): calc. C 75.6 H 5.56 found C 75.5 H 5.60. - IR: 3420 cm⁻¹ (OH). - UV (MeOH) X max (loge): 212 (4.26), 246 (4.58), 301 (4.06), 311 nm (4.08). - ²H-NMR: δ(ppm) = 3.82 (s; 3H, -OCH₃), 3.90 (s; 3H, -OCH₃), 6.82 (s; 1H, -OH), 7.00-7.70 (m; 6H, aromat.), 9.18 (d; J = 3 Hz, 1H, H₅). - MS (70 eV): m/z = 254 (M⁺, 100 %), 239 (100 %, *224.89), 211 (28 %), 196 (20 %), 168 (16 %).

Mixture of 19 and 20: 0.31 g (1 mmol) 18 in 15 ml absol. toluene and 0.1 ml ECF were stirred for 1 h at room temp. After evaporation, 19 and 20 were separated from the residue by preparative tlc (Kieselgel, ether).

2-Ethoxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (23)

0.62 g (3 mmol) 1 in 10 ml absol. toluene and 0.29 g (3 mmol) ECF were heated on a steam bath for 2 h. After cooling, the filtrate (precipitate of 1-HCl) was concentrated and purified by column chromatography: colourless amorphous solid (0.41 g), mp. 70° (ether). C₁₄H₁₉NO₄ (265.3): calc. C 63.4 H 7.23 found C 63.2 H 7.17. - IR: 1700 cm⁻¹ (CO). - ¹H-NMR (signals of 19 are omitted): δ(ppm) = 1.27 (t; J = 7 Hz, 3H, -CH₂-CH₃), 2.53 (s; 3H, -NCH₃), 4.10 (q; J = 7 Hz, 2H, -CH₂CH₃). - MS-FD: m/z = 254 (20) and m/z = 383 (19).

2-Ethoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (24)

0.15 g (1 mmol) 10 in 10 ml absol. CH₂Cl₂, 0.1 g NaHCO₃ and 0.1 ml (1 mmol) ECF were refluxed for 12 h. After filtration, the mixture was concentrated and purified by column chromatography: 0.15 g
(75 %) 24. - IR: 1705 cm\(^{-1}\) (CO). - \(^1\)H-NMR: \(\delta\text{(ppm)} = 1.27\ (t; J = 7\ Hz, 3H, -CH\_2-CH\_3), 2.77\ (t; J = 6\ Hz, 2H, -CH\_2-CH\_2-N), 3.63\ (t; J = 6\ Hz, 2H, -CH\_2-CH\_2-N), 4.15\ (q; J = 7\ Hz, 2H, -CH\_2-CH\_3), 4.53\ (s; 2H, -CH\_2-N), 6.90-7.27\ (m; 4H, aromat.).

2-(2,2,2-Trichloroethoxycarbonyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (25)

25 was gained by the procedure described for 1 to 23 from 0.83 g (4 mmol) 1 and 0.55 ml (4 mmol) 2,2,2-trichloroethylchloroformate. Colourless solid: 0.63 g (53 %), mp. 114° (ether). C\(_{14}\)H\(_{16}\)C\(_{3}\)N\(_4\)O\(_4\) (297.8): calc. C 45.6 H 4.38 found C 46.1 H 4.79. - IR: 1710 cm\(^{-1}\) (CO). - \(^1\)H-NMR: \(\delta\text{(ppm)} = 2.80\ (t; J = 6\ Hz, 2H, -CH\_2-CH\_2-N), 3.77\ (t; J = 6\ Hz, 2H, -CH\_2-CH\_2-N), 3.83\ (s; 6H, -OCH\_3), 4.62\ (broad s; 2H, -CH\_2-CC\(_3\)), 4.73\ (s; 2H, -CH\_2-N), 6.57 and 6.60\ (2 x s; 2H, aromat.).

1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline (26)

0.45 g (1.5 mmol) 25 in 3 ml dioxane and 8 ml glacial acetic acid were stirred with 0.8 g zinc dust for 4 h at room temp., the filtrate was strongly basified with 20 % NaOH and extracted with chloroform. The organic layer was removed to give 26. Colourless oil: 0.18 g (63 %), bp: 116-117°. - IR: 3160-3380 cm\(^{-1}\) (NH). - \(^1\)H-NMR: \(\delta\text{(ppm)} = 1.67-3.27\ (m; 6H, -CH\_2-N), 2.10\ (s; 1H, -NH), 3.77\ (s; 6H, -OCH\_3), 6.47\ and 6.63\ (2 x s; 2H, aromat.).

23 from 26

A mixture of 0.29 g (1.5 mmol) 26 in 4 ml CHCl\(_3\)/ether 1:1, 4 ml 15 % KOH and 0.5 ml ECF was refluxed for 2 h. Another 4 ml 15 % KOH and 0.5 ml ECF and, 2 h later, 2 ml 15 % KOH were added. After 1 h the organic layer was separated and concentrated to give 23 in 92 % yield. Physical data: see 23 from 1.

References

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