3,6-Bis(trifluormethyl)-1,2,4-triazin-5-carbaldehyd-N,N-dimethylhydrazon **(12)**

1,09 g (5 mmol) **1** werden mit 355 mg (2,5 mmol) **10** in CCl_4 unter Feuchtigkeitsausschluß 15 h unter Rückfluß erhitzt. Die entfärbte Lösung wird eingeengt und an Kieselgel F(30 × 2 cm, n-Pentan/Chloroform 8:2) chromatographiert. Man eluiert eine intensiv gelbe Fraktion, die aus Petrolether (40–60°) umkristallisiert wird. Ausb. 265 mg (37 %, ber. auf **10**); Schmp. 95° (Petrolether). – IR (KBr): 2930, 1550, 1520, 1490, 1450, 1425, 1410, 1405, 1350, 1310, 1260, 1220, 1165, 1130, 1070, 1035, 990, 860, 830, 820, 790, 770, 730, 715, 655, 635 cm^{-1}. – UV (CH_2Cl_2): λ_{max}(lgε) = 387 (4.36), 239 nm (3.40). – ^{1}H-NMR (CCl_4): δ(ppm) = 6.97 (s, 1H, CH), 3.43 (s, 6H, $N(CH_3)_2$). – MS (70 eV): m/z = 287 (84 %, M^+), 43 (100 %). – $C_8H_7F_6N_5$ (287.18) Ber. C 33.5 H 2.44 N 24.4 Gef. C 33.7 H 2.29 N 24.3.

Literatur

1 M.G. Barlow, R.N. Haszeldine und J.A. Picket, J. Chem. Soc. Perkin Trans. 1 *1978,* 378.
2 Zusammenfassungen: J. Sauer, Angew. Chem. *79,* 76 (1967); Angew. Chem. Int. Ed. Engl. *6,* 16 (1967); D.L. Boger, Tetrahedron *39,* 2869 (1983); E.G. Kovalev, I.Ya. Postovskii, G.L. Rustinov und I.L. Shegal, Khim. Geterotsikl. Soedin. *1981,* 1462; C.A. *96,* 688509 (1982); J. Sauer und R. Sustmann, Angew. Chem. *92,* 773 (1980); S.M. Weinreb und J.I. Levin, Heterocycles *12,* 949 (1979); S.M. Weinreb und R.R. Staib, Tetrahedron *38,* 3087 (1982).
3 G. Seitz, R. Dhar und W. Hühnermann, Chem. Ztg. *106,* 100 (1982) und dort zit. Lit.
4 G. Seitz, R. Dhar und S. Dietrich, Arch. Pharm. (Weinheim) *316,* 472 (1983).
5 G. Seitz, R. Dhar, R. Mohr und W. Overheu, Arch. Pharm. (Weinheim) *317,* 237 (1984).
6 Dargestellt nach E.J. Corey und D. Enders, Chem. Ber. *111,* 1337 (1978).

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Arch. Pharm. (Weinheim) *319,* 694–704 (1986)

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)/$NaBH_3CN$ 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 80. anniversary.

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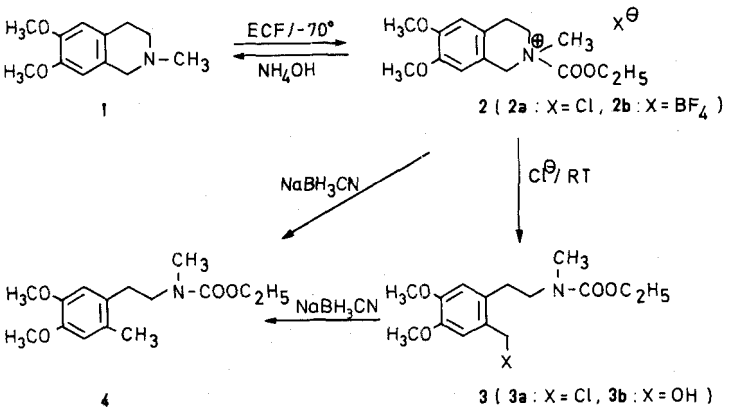
9. The reaction with ECF/$NaBH_3CN$ followed by $LiAlH_4$ reduction is a versatile approach to *Emde* degradation products avoiding strongly basic conditions and elevated temperature. Cleavage reactions of other α-amino ethers, e.g. thebaine **(18)**, and *N*-demethylation reactions of the tetrahydroisoquinolines **1** and **10** with ECF are reported.

Reduzierende α-Aminoether-Spaltung unter milden Bedingungen

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methylisochinolin **(1)** wird mit Chlorameisensäureethylester (ECF)/$NaBH_3CN$ über das quartäre Urethan **2** zum 2-[(β-*N*-Ethoxycarbonyl-*N*-methyl)-aminoethyl]-4,5-dimethoxytoluol **(4)** umgesetzt. – Dieses Verfahren führt von Laudanosin **(5)** zum Dibenzyl-Derivat **9.** – Die ECF/$NaBH_3CN$-Reaktion, kombiniert mit der $LiAlH_4$-Reduktion der tert. Urethane, ist eine Alternative zum *Emde*-Abbau und vermeidet stark basische Bedingungen und erhöhte Temp. Die Spaltung weiterer α-Aminoether, u.a. Thebain **(18)**, und *N*-Demethylierungen der Tetrahydroisochinoline **1** und **10** werden beschrieben.

C-1-N bond cleavage of the tetrahydroisoquinoline system has been accomplished by various methods, e.g. *Hofmann*-degradation[1], Pt-catalyzed hydrogenation[2] or reductive cleavage with Na-amalgam after quaternization (*Emde*-degradation)[3], using cyanogen bromide[4] and ethylchloroformate (ECF), introduced into the chemistry of *N*-alkylated 1,2,3,4-tetrahydroisoquinolines by *Gadamer*[5]. This paper is concerned with a modified ECF-method. Recently *Calverley*[6] has described a reductive benzylamine cleavage of the carboline ring system with ECF in absol. THF at –70 °C followed by $NaBH_3CN$ at room temp. He discusses the participation of $H^{\ominus}$ as a nucleophile. This can be interpreted as a S_N-reaction of $H^{\ominus}$ at the benzylic C-atom of a quaternary urethane.

Benzylchlorides have been reduced to toluenes[7] using $NaBH_3CN$. This leads to the suggestion that nucleophilic attack of $Cl^{\ominus}$ 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.



1 — 2 (**2a** : X = Cl , **2b** : X = BF_4) — 4 — 3 (**3a** : X = Cl , **3b** : X = OH)

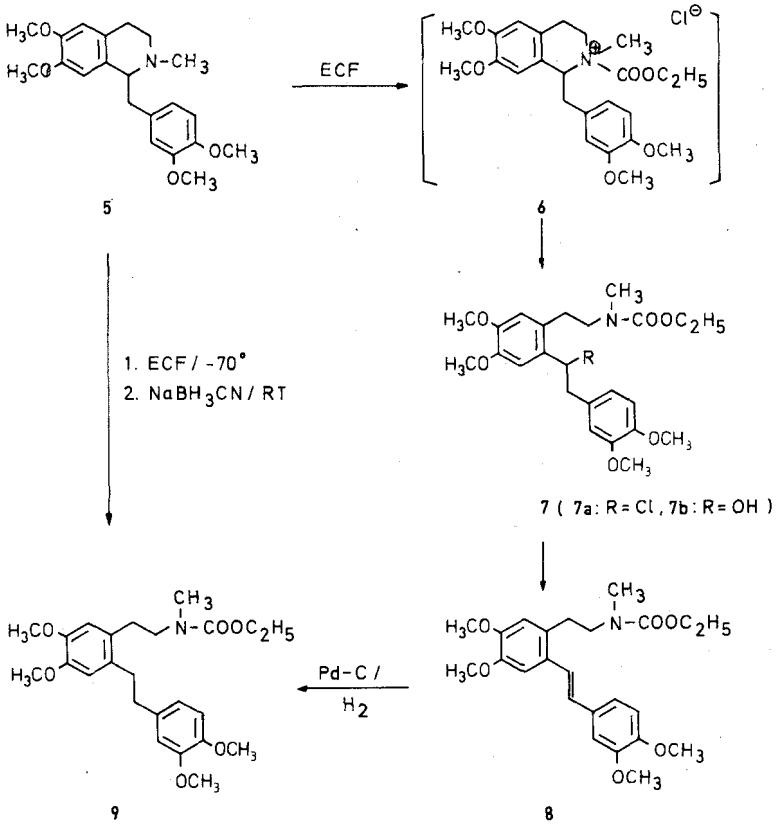
Scheme 1

Quaternary urethanes of type **2a** are known to be very sensitive to temp. and to moisture, but they can be isolated under special conditions[8]. 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.[8]: 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 $NaBH_3CN$ at room temp. and to **3b** by water.

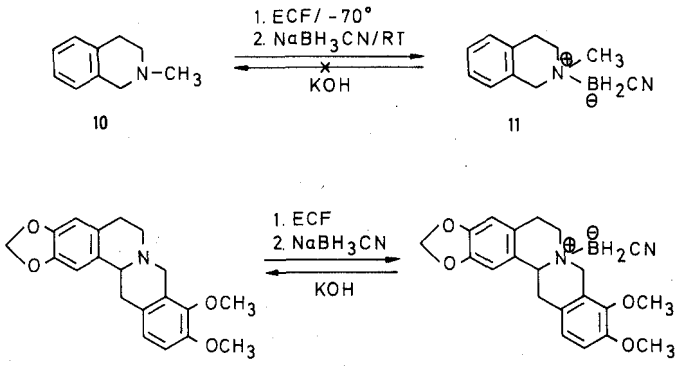
$LiAlH_4$ reduces the benzylchloride- and the urethane- moiety in **3a** leading to 2-(β-dimethylaminoethyl)-4,5-dimethoxytoluene, isolated as its HCl-salt (mp. 195°).

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 $NaBH_3CN$. 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 $NaBH_3CN$ 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_4OH.



Scheme 2

When *Gadamer* and *Knoch*[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*[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° in the presence of $AgBF_4$ (compare **2a** → **2b**), a double salt $\mathbf{5}_2 \cdot AgBF_4$ was isolated. Treatment of **5** with ECF at –70° for 30 min. followed by addition of cold $AgBF_4$ in THF and work-up at room temp. led to stilbene **8. 7a** was hydrolyzed to **7b, 7a** splits off HCl to **8**[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 $LiAlH_4$ to *N,N*-dimethylamines[9], the overall reactions **1** → **4** and **5** → **9** are mild alternatives to the *Emde*-degradation[3] which needs strong alkali at elevated temp. **1** and **5** are phenylogous α-aminoethers. The unsubstituted tetrahydroisoquinoline **10,** however, is reported not to react with ECF/$OH^{\ominus}$[10] and, contrary to **1,** no C-1-N bond cleavage is observed with ECF/$NaBH_3CN$. We got the cyanoborane adduct **11,** normally obtained from tert. amines and $NaBH_3CN$ in THF[11] (scheme 3).



10 **11**

12 **13**

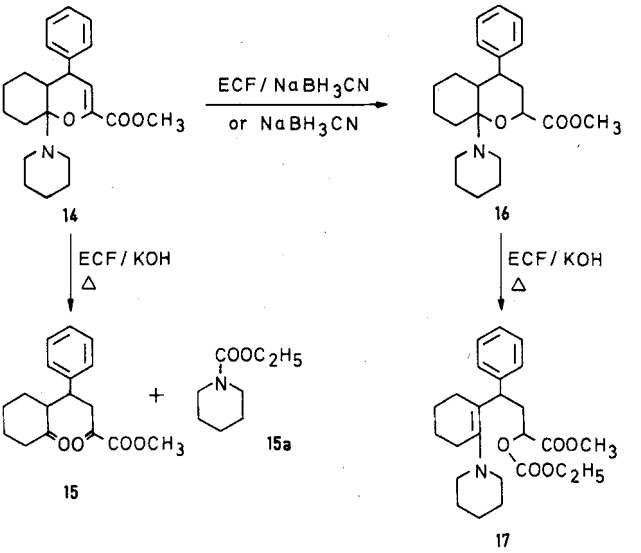
Scheme 3

Knabe and *Shukla*[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 +M-effect of the methoxygroups of **1** which could stabilize a transition state with a positively charged benzylic 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 α-aminoethers inaugurated experiments with the α-aminoethers **14** and **16,** respectively*. **14** was converted to the ketoester **15** by ECF/KOH, probably *via* quaternization, formal nucleophilic substitution by $OH^{\ominus}$ and

*) 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).)

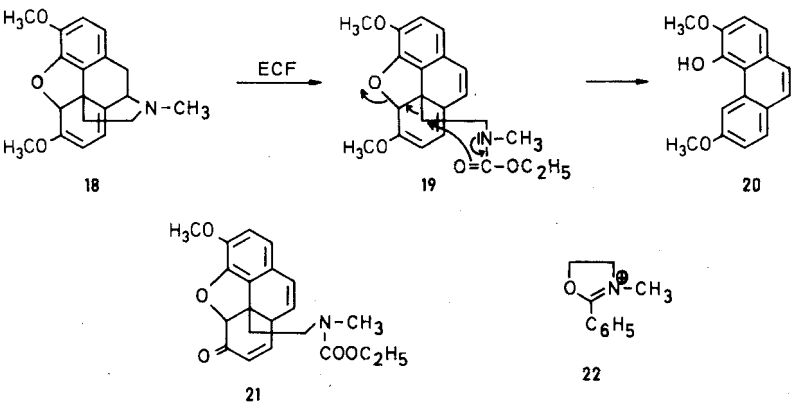
successive tautomerization. On the other hand, **14** was only reduced with ECF/$NaBH_3CN$ or $NaBH_3CN$ to its dihydro-derivative **16**, which was, however, cleaved with ECF/KOH to the ester **17** (Scheme 4).



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.**

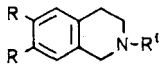
Phenylogous α-aminoethers are expected to resemble their vinylogous analogues. When thebaine **(18),** a twofold vinylogous α-aminoether, was treated with ECF in boiling toluene, thebaol **(20)** arose as the main product, whilst at 0° **19** was dominant. **19** was separated from **20** by tlc, but 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



Scheme 5

al.[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.[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[14], especially, if the N-CH_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_2CCl_3 instead of ECF. **25** is easily reduced by Zn/acetic acid[15] to **26,** which is then converted to **23** by ECF (Scheme 6).



	R	R'
23	OCH_3	$COOC_2H_5$
24	H	$COOC_2H_5$
25	OCH_3	$COOCH_2CCl_3$
26	OCH_3	H

Scheme 6

Experimental Section

MP: Büchi SMP-20 apparatus, uncorr. *Elementary Analysis:* Microanalysis Laboratory of University Regensburg. *IR Spectra:* Beckman Acculab III. – *^{1}H-NMR Spectra:* Bruker WH 90 (90 MHz) and Bruker Spectrospin (250 MHz) in $CDCl_3$, 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), $CHCl_3$/ether 1:1 as eluent. – All reactions were performed under N_2.

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

2a: 0.21 g (1 mmol) **1**[16] in 5 ml absol. CH_2Cl_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[8]: CO-band at 1820 cm^{-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 $AgBF_4$ was added and stirred for 30 min at –70°. The solid (mixture of **2b** and AgCl) was washed with THF. IR: 1820 cm^{-1} (CO). – ^{1}H-NMR: δ(ppm) = 1.27 (t; J = 7 Hz, 3H, -CH_2-$\underline{CH_3}$), 2.87–3.27 (m; 4H, -CH_2-CH_2-N-), 3.47 (s; 2H, -CH_2-N-), 3.73 (s; 3H, -NCH_3), 3.77 and 3.80 (2 × s; 6H, –OCH_3), 4.50 (q; J = 7 Hz, 2H, -$\underline{CH_2}$-CH_3), 6.67 (s; 2H, aromat.).

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

0.62 g (3 mmol) **1**[16] in 10 ml absol. CH_2Cl_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^{-1} (CO). – ^{1}H-NMR: δ(ppm) = 1.23 (t; J =

7 Hz, 3H, $-CH_2-CH_3$), 2.77–3.63 (m; 4H, $-CH_2-CH_2$), 2.87 (s; 3H, $-NCH_3$), 3.83 (s; 6H, $-OCH_3$), 4.10 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 4.60 (s; 2H, $-CH_2Cl$), 6.63 (broad s; 1H, aromat.), 6.77 (s; 1H, aromat.).

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). – ^{1}H-NMR: δ(ppm) = 1.20 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.70–3.67 (m; 4H, $-CH_2-CH_2-$), 2.85 (s; 3H, $-NCH_3$), 3.83 (s; 6H, $-OCH_3$), 4.05 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 4.60 (s; 2H, $-CH_2OH$), 6.63 and 6.87 (2 × s; 2H, aromat.).

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

0.31 g (1.5 mmol) **1**[16] and 0.6 ml (6 mmol) ECF in 15 ml absol. THF were stirred at –70° for 1h. Then dropwise addition of 0.19 g (3 mmol) $NaBH_3CN$ 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). – ^{1}H-NMR: δ(ppm) = 1.23 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.25 (s; 3H, $-CH_3$), 2.62–3.53 (m; 4H, $-CH_2-CH_2-$), 2.85 (s; 3H, $-NCH_3$), 3.83 (s; 6H, $-OCH_3$), 4.08 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 6.62 and 6.63 (2 × s; 2H, aromat.). – MS (70 eV): m/z = 281 ($M^{+\cdot}$, 41 %), 253 (4 %), 236 (5 %), 178 (74 %), 165 (94 %), 164 (22 %), 151 (16 %), 116 (100 %), 91 (9 %), 72 (17 %), 44 (89 %) (for interpretation see[17]).

4 *from* **3a**

0.2 g $NaBH_3CN$ 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. CH_2Cl_2 and an excess $AgBF_4$ 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°. $C_{42}H_{54}N_2O_8 \cdot AgBF_4$ (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} (BF_4^-). – ^{1}H-NMR (CF_3COOD): δ(ppm) = 2.53–3.27 (m; 14H), 3.33 (s; 6H, $-NCH_3$), 3.47 (s; 6H, $-OCH_3$), 3.53 (s; 18H, $-OCH_3$), 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. $CHCl_3$) λ max (qual.): 246, 283 nm. – ^{1}H-NMR: δ(ppm) = 1.23 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.50–3.57 (m; 6H, $-CH_2-$), 2.83 (s; 3H, $-NCH_3$), 3.80 (s; 3H, $-OCH_3$) 3.88 (s; 3H, $-OCH_3$), 3.92 (s; 3H, $-OCH_3$), 3.98 (s; 3H, $-OCH_3$), 4.17 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 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 ($M^{+\cdot}$), 429 ($M^{+\cdot}$-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]).

1-[2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)-ethane **(9)**

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°. Then 0.13 g (2 mmol) $NaBH_3CN$ in 30 ml absol. 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). $C_{24}H_{33}NO_6$ (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 ε): 207 (4.50), 227 (4.27), 279 nm (3.85). – ^{1}H-NMR: δ(ppm) = 1.20 (t; J = 7 Hz, 3H, -CH_2-$\underline{CH_3}$), 2.60–3.53 (m; 4H, -CH_2-CH_2-N-), 2.83 (s; 7H, -NCH_3, -CH_2-CH_2-Ar.), 3.79 (s; 3H, -OCH_3), 3.81 (s; 3H, -OCH_3), 3.83 (s; 6H, -OCH_3), 4.10 (q; J = 7 Hz, 2H, -$\underline{CH_2}$-CH_3), 6.60, 6.63, 6.72 and 6.75 (4 × s; 5H, aromat.).

from **8:** 0.43 g (1 mmol) **8**[5] in 30 ml $CHCl_3$ were hydrogenated with 0.3 g 10 % Pd/C at room temp. for 2 h. 64 % **9.**

1,2,3,4-Tetrahydro-2-methylisoquinoline-cyanoborane **(11)**

11 was obtained as a colourless amorphous solid by treating 0.29 g (2 mmol) **10**[18] in 5 ml absol. THF with 0.8 ml (8 mmol) ECF at –70°, then adding 0.26 g (4 mmol) $NaBH_3CN$ in 50 ml absol. THF. For working-up see **5** to **9:** 0.25 g (67 %), mp. 97° (ether). $C_{10}H_{13}N \cdot {}^{11}BH_2CN$ (186.1): calc. C 71.0 H 8.14 found C 70.9 H 8.21. – IR: 2400 (BH), 2260 cm^{-1} (CN). – ^{1}H-NMR: δ(ppm) = 2.70 (s; 3H, –NCH_3), 2.83–3.43 (m; 4H, -CH_2-CH_2-), 3.90 and 4.30 (AB; J = 15 Hz, 2H, -CH_2-), 6.90–7.27 (m; 4H, aromat.). – MS (~10 eV): m/z = 186 $M^{+\cdot}$, 24 %), 185 (17 %), 184 (14 %), 183 (4 %), 159 (100 %), 158 (27 %), 147 (42 %), 146 (20 %), 131 (9 %), 105 (17 %), 104 (16 %).

Tetrahydroberberine-cyanoborane **(13)**

0.34 g (1 mmol) tetrahydroberberine **(12)**[19] in 10 ml absol. THF were treated with 0.4 ml (4 mmol) ECF and 0.13 g (2 mmol) $NaBH_3CN$ according to the procedure given for **9** from **5**. Colourless amorphous solid: 0.29 g (76 %), mp. 181–182° (methanol). $C_{20}H_{21}NO_4 \cdot {}^{11}BH_2CN$ (378.3): calc. C 66.7 H 6.14 found C 66.7 H 6.04. – IR: 2480 (BH), 2220 cm^{-1} (CN). – UV (MeOH) λ max (log ε): 212 (4.21), 228 (sh), 286 nm (3.65). – ^{1}H-NMR: δ(ppm) = 2.63–4.23 (m; 8H, -CH_2-), 3.83 (s; 3H, -OCH_3), 3.88 (s; 3H, -OCH_3), 4.70 (d; 1H, -CH-), 5.92 (s; 2H, -O-CH_2-O-), 6.60, 6.70 and 6.87 (3 × s; 4H, aromat.). – MS (70 eV): m/z = 378 ($M^{+\cdot}$, 13 %), 339 (100 %, *304.02), 338 (54 %), 308 (17 %, *279.83), 180 (8 %), 178 (19 %), 164 (89 %), 149 (51 %, *135.37).

Tetrahydroberberine **(12)** *from* **13**

Refluxing **13** in a mixture of methanol/20 % KOH (2:1) for 2 h yields **12.** mp. 168° (167°[20]).

α-*Keto-γ-phenyl-γ-(2'-oxocyclohexenyl)-methylbutyrate* **(15)**

0.36 g (1 mmol) **14** in 10 ml CH_2Cl_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°, $C_{17}H_{20}O_4$ (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 (logε): 206 (3.94), 250–270 nm (sh). – ^{1}H-NMR (250 MHz): δ(ppm) = 1.57–3.74 (m; 12 H), 3.80 (s; 3H, -$COOCH_3$), 7.12–7.33 (m; 5H, -C_6H_5). – MS (70 eV): m/z = 288 ($M^{+\cdot}$, 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 sample[21].

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. CH_2Cl_2 were reacted with 0.2 ml (2 mmol) ECF for 1 h at –70°, then 0.1 g $NaBH_3CN$ 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). – ^{1}H-NMR: δ(ppm) = 0.93–3.43 (m; 23 H), 3.77 (s; 3H, -$COOCH_3$), 7.03–7.70 (m; 5H, -C_6H_5). – MS (70 eV): m/z = 357 ($M^{+\cdot}$, 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(1')-yl)-methylbutyrate* **(17)**

A mixture of 0.07 g (0.2 mmol) **16** in 5 ml absol. CH_2Cl_2, 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) λ max (qual.): 202, 250–270 nm (sh). – ^{1}H-NMR (250 MHz): δ(ppm) = 1.30 (t; J = 6.9 Hz, 3H, -CH_2-$\underline{CH_3}$), 1.35–3.00 (m; 22H), 3.77 (s; -OCH_3), 4.16 (q; J = 6.9 Hz, 2H, –$\underline{CH_2}$-CH_3), 7.11–7.28 (m; 5H, -C_6H_5). – MS (70 eV): m/z = 370 (3 %), 341 (27 %), 340 (100 %), 281 (11 %), 270 (9 %), 149 (23 %), 124 (20 %). – MS-FD: m/z = 429 ($M^{+\cdot}$).

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 conc. residue with column chromatography (Kieselgel, $CHCl_3$): yellow solid: 0.14 g (55 %), mp. 93–94°; (92.5–93.5°[13]). $C_{16}H_{14}O_3$ (254.3): calc. C 75.6 H 5.56 found C 75.5 H 5.60. – IR: 3420 cm^{-1} (OH). – UV (MeOH) λ max (logε): 212 (4.26), 246 (4.58), 301 (4.06), 311 nm (4.08).- ^{1}H-NMR: δ(ppm) = 3.82 (s; 3H, -OCH_3), 3.90 (s; 3H, -OCH_3), 6.82 (s; 1H, -OH), 7.00–7.70 (m; 6H, aromat.), 9.18 (d; J = 3 Hz, 1H, H_5). – MS (70 eV): m/z = 254 ($M^{+\cdot}$, 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).

20: see above. **19** + **20:** IR: 1700 cm^{-1} (CO). – ^{1}H-NMR (signals of **19** are omitted): δ(ppm) = 1.27 (t; J = 7 Hz, 3H, -CH_2-$\underline{CH_3}$), 2.53 (s; 3H, -NCH_3), 4.10 (q; J = 7 Hz, 2H, -$\underline{CH_2}$-CH_3). – MS-FD: m/z = 254 **(20)** and m/z = 383 **(19).**

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 ml (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). $C_{14}H_{19}NO_4$ (265.3): calc. C 63.4 H 7.23 found C 63.2 H 7.17. – IR: 1700 cm^{-1} (CO). – ^{1}H-NMR: δ(ppm) = 1.37 (t; J = 7 Hz, 3H, -CH_2-$\underline{CH_3}$), 2.83 (t; J = 6 Hz, 2H, -$\underline{CH_2}$-CH_2-N-), 3.73 (t; J = 6 Hz, 2H, -CH_2-$\underline{CH_2}$-N-), 3.90 (s; 6H, -OCH_3), 4.23 (q; J = 7 Hz, 2H, -$\underline{CH_2}$-CH_3), 4.60 (s; 2H, -CH_2-), 6.63 and 6.67 (2 × s; 2H, aromat.). – MS (70 eV): m/z = 265 ($M^{+\cdot}$, 32 %), 236 (100 %), *210.17), 192 (23 %, *156.20), 177 (6 %, *163.17), 176 (7 %), 164 (19 %), 149 (6 %, *135.37), 144 (12 %).

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

0.15 g (1 mmol) **10** in 10 ml absol. CH_2Cl_2, 0.1 g $NaHCO_3$ 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: δ(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-), 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), $C_{14}H_{16}Cl_3NO_4$ (297.8): calc. C 45.6 H 4.38 found C 46.1 H 4.79. – IR: 1710 cm^{-1} (CO). – ^{1}H-NMR: δ(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-CCl_3), 4.73 (s; 2H, -CH_2-), 6.57 and 6.60 (2 × 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_1 116–117°. – IR: 3160–3380 cm^{-1} (NH). – ^{1}H-NMR: δ(ppm) = 1.67–3.27 (m; 6H, -CH_2-), 2.10 (s; 1H, -NH), 3.77 (s; 6H, -OCH_3), 6.47 and 6.63 (2 × 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

1 A.R. Battersby and B.J.T. Harper, J. Chem Soc. *1962,* 3526.
2 H. Emde and H. Kull, Arch. Pharm. (Weinheim) *274,* 173 (1936).
3 H. Emde and H. Kull, Arch. Pharm. (Weinheim) *272,* 469 (1934).
4 S. Prior and W. Wiegrebe, Arch. Pharm. (Weinheim) *314,* 577 (1981).
5 J. Gadamer and F. Knoch, Arch. Pharm. (Weinheim) *259,* 135 (1921).
6 M.J. Calverley, J. Chem. Soc. Chem. Commun. *1981,* 1209.
7 a) R.O. Hutchins, B.E. Maryanoff and C.A. Milewski, J. Chem. Soc. Chem. Commun. *1971.* 1097; b) S.G. Kim, Y.J. Kim and K.H. Ahn, Tetrahedron Lett. *24,* 3369 (1983).
8 a) D. Cook, Canad. J. Chem. *40,* 2362 (1962); b) H. Böhme und G. Lerche, Liebigs Ann. Chem. *705,* 154 (1967).
9 F. v. Bruchhausen and J. Knabe, Arch. Pharm. (Weinheim) *287,* 601 (1954).
10 J. Knabe, Arch. Pharm. (Weinheim) *289,* 479 (1956).
11 a) C. Weidig, S.S. Uppal and H.C. Kelly, Inorg. Chem. *13,* 1763 (1974); b) S.S. Uppal and H.C. Kelly, J. Chem. Soc. Chem. Commun. *1970,* 1619.
12 J. Knabe and U.R. Shukla, Arch. Pharm. (Weinheim) *295,* 690, 871 (1962).
13 C. Bertgen, W. Fleischhacker and F. Vieböck, Chem. Ber. *100,* 3002 (1967).
14 a) G. Kraiss and K. Nador, Tetrahedron Lett. *1971,* 57; b) D.L. Trepanier and S. Sunder, J. Med. Chem. *16,* 342 (1973).
15 W.J. Kim, D.U. Lee and W. Wiegrebe, Arch. Pharm. (Weinheim) *317,* 438 (1984).
16 E. Späth and H. Epstein, Chem. Ber. *59,* 2791 (1926).

17 W. Wiegrebe, J. Fricke, H. Budzikiewicz and L. Pohl, Tetrahedron *28*, 2849 (1972).
18 S. Kubota, T. Masui, E. Fujita and S.M. Kupchan, J. Org. Chem. *31*, 516 (1966).
19 I. Sallay and R.H. Ayers, Tetrahedron *19*, 1397 (1963).
20 H.W. Bersch and W. Seufert, Chem. Ber. *70*, 1121 (1937).
21 C. Schotten, Chem. Ber. *15*, 421 (1882).

[Ph 113]

Arch. Pharm. (Weinheim) *319*, 704–715 (1986)

Oxabenzomorphane: Synthese von 4-Phenyl-tetrahydropyran-2-carbonsäuren[1)]

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Durch [4+2]-Cycloaddition der Enamine **6a–6f** mit den Benzylidenbrenztraubensäureestern **7a–7g** entstehen die 6-Amino-4-phenyl-dihydropyran-2-carbonsäureester **8a–8p.** Aus **8d** wird durch Hydrolyse, Wasserabspaltung und katalytische Hydrierung die 4-Phenyl-tetrahydropyran-2-carbonsäure **12a** gewonnen.

Oxabenzomorphanes: Synthesis of 4-Phenyltetrahydropyran-2-carboxylic acid

[4+2]-Cycloaddition of the enamines **6a–6f** with the benzylidenepyruvic acid esters **7a–7g** result in the formation of the 6-amino-5-phenyldihydropropane-2-carboxylic acid esters **8a–8p.** The 4-phenyltetrahydropyran-2-carboxylic acid **12a** can be obtained from **8d** by hydrolysis, dehydrogenation and catalytic hydrogenation.

Einige 2,6-Methano-tetrahydro-3-benzazocine, besser bekannt als 6,7-Benzomorphane, sind wertvolle Arzneimittel. Diese vom Morphin abgeleiteten Substanzen können bei starker analgetischer Aktivität einen mehr oder weniger ausgeprägten Morphinantagonismus zeigen[2)]. Ein Beispiel ist Pentazocin **(1),** das in der Bundesrepublik als Fortral® im Handel ist[3)].

Wenig untersucht wurden bisher Oxa-Derivate von Benzomorphanen: *Zaugg* und Mitarb. haben die Synthese von 2,6-Methano-1,4-benzoxazocinen **2** (R=H,Alkyl) aus Chroman-Derivaten beschrieben[4)5)]; Derivate von **2** haben im Tierversuch analgetische Aktivität gezeigt[4)]. In den letzten Jahren wurde auch von Oxamorphinanen berichtet[6)]: das Proxorphan **(3)** z.B. soll starke analgetische und antitussive Eigenschaften besitzen[6)].

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