130)

Ring-cleavage of Phthalidisoquinoline Alkaloids by Ethyl Chloroformate*)**)

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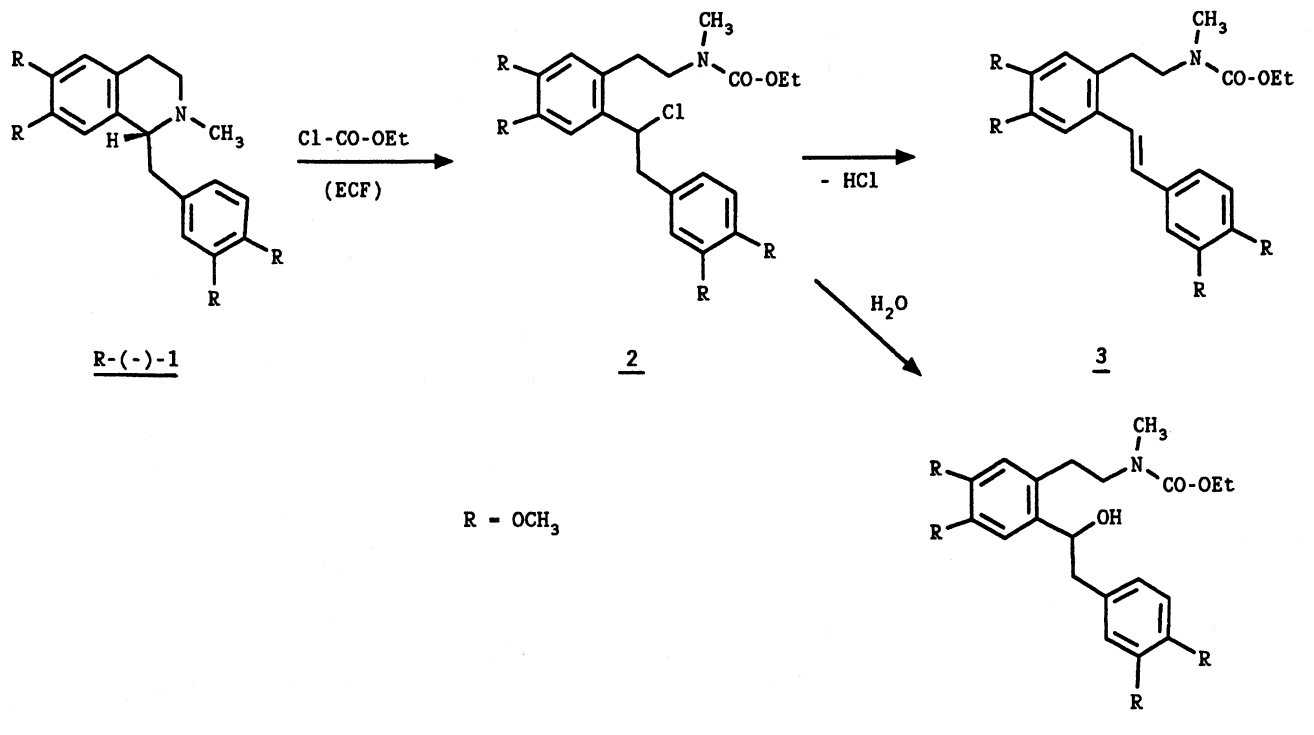
Degradation of (-)-α-narcotine (**5**), (-)-β-narcotine (**6**), and (-)-β-hydrastine (**7**) with ethyl chloroformate (ECF) affords the chloro-urethans **9** and **18**, respectively. Diastereomer **9**-I is easily hydrolyzed to the hydroxy-urethan **10**, whilst **18** is converted to the methoxy-analogue **19**. The stilbene lactone **11** is obtained from **9**-I by treatment with DBU, the analogous stilbene **17** arises already when **7** is reacted with ECF. - Hydroxy-urethan **10** - a phenylogous aldol - is split by OH^- to aldehyde **13** and to meconine (**14**). $LiAlH_4$-reduction of **10** yields the stereochemically homogenous triol **15**, which is cyclized to diastereomers of the 3-phenyl-isochroman **16** under acidic conditions.

Ringöffnung von Phthalidisochinolin-Alkaloiden durch Chlorameisensäureethylester

Der Abbau von (-)-α-Narkotin (**5**), (-)-β-Narkotin (**6**) und (-)-β-Hydrastin (**7**) mit Chlorameisensäureethylester (ECF) führt zu den Chlorurethanen **9** bzw. **18**. Das Diastereomer **9**-I reagiert leicht zum Hydroxyurethan **10**, **18** zum Methoxy-Analogen **19**. Chlorurethan **9**-I bildet mit DBU das Stilbenlacton **11**, aus **7** entsteht das analoge Stilben **17** bereits beim ECF-Abbau. - Hydroxyurethan **10** (ein phenyloges Aldol) wird durch Basen zum Aldehyd **13** und Mekonin (**14**) gespalten. $LiAlH_4$ reduziert **10** zum sterisch einheitlichen Triol **15**, das H^+-katalysiert zu Diastereomeren des 3-Phenylisochromans **16** zyklisiert wird.

Gadamer and *Knoch*[1] have introduced ethyl chloroformate (ECF) for the benzylic cleavage of *N*-alkylated 1,2,3,4-tetrahydroisoquinolines; *von Bruchhausen* and *Knabe*[2] have overcome the obstacle[1] that the urethan moiety so obtained could not be hydrolyzed to the corresponding secondary amine by reducing the carbamate with $LiAlH_4$, and *Knabe* and *Shukla*[3] have studied the electronic requirements for the cleavage of benzylamines in general. Some more aspects of *von Bruchhausen's* experiments are compiled in a review[4].

We have repeated[5] *Gadamer's* experiments with laudanosine (**1**) and isolated the chloro-urethan **2**, the intermediate in the formation of stilbene **3** from laudanosine (**1**)[1,2] as postulated by *Gadamer*[1]. Neither the absolute configuration nor the optical purity of chloro-urethan **2** could be deter-



Scheme 1

*) Part of the PhD-thesis *S. von Angerer*, née *Prior*, Regensburg, 1980.
**) Dedicated with warm regards to Prof. Dr. *J. Sauer*, Regensburg, on the occasion of his 60. birthday.

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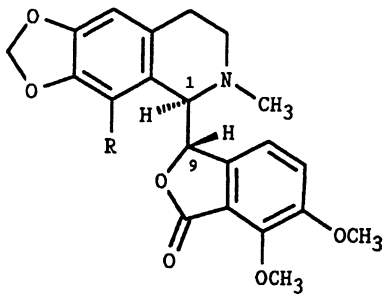
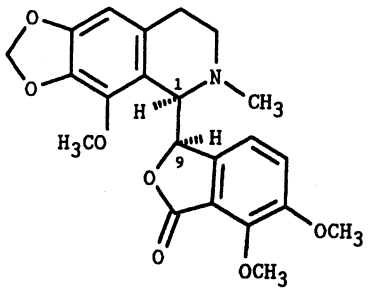


5: R = OCH_3 [(-)-5: 1R,9S]

7: R = H [(-)-7: 1R,9S]



6 [(-)-6: 1R,9R]

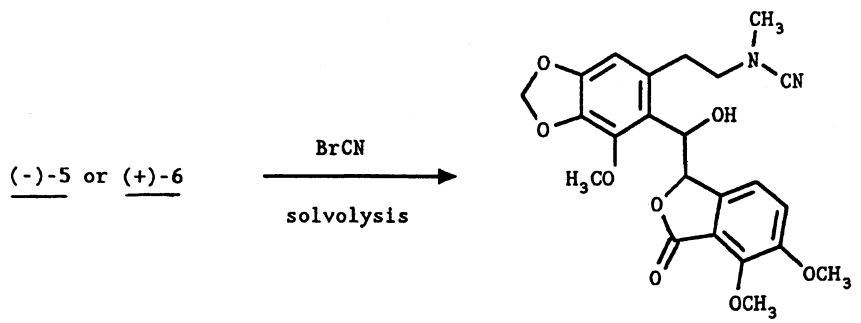
Scheme 2

mined up to now (vide infra). The hydroxy-urethan **4** was obtained from **2** by hydrolysis or under more vigorous conditions with ECF from **1** with a 47:53-ratio of enantiomers[5].

These findings prompted us to study the degradation of α-narcotine (**5**), β-narcotine (**6**), and β-hydrastine (**7**); these alkaloids are characterized by an additional centre of chirality in their lactone parts (C-9), in direct neighbourhood of the chiral centre under consideration.

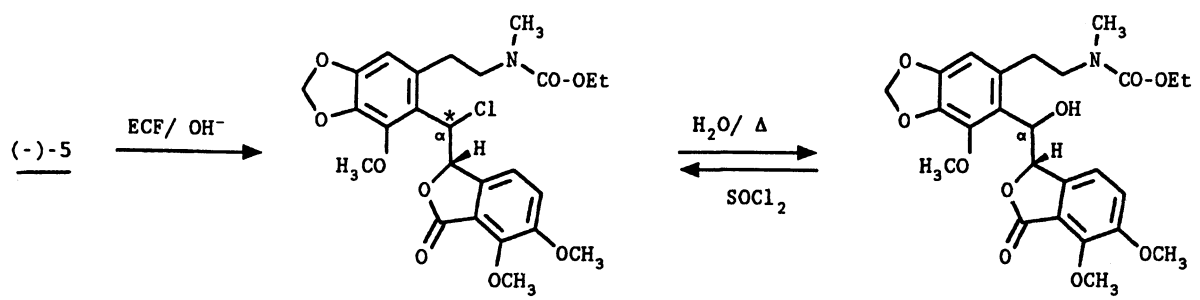
A similar reaction has been performed with (-)-α-**5** and (+)-β-narcotine (**6**), respectively, by *Kerekes, Gaál*, et al.[6] using BrCN: under solvolytic conditions they obtained the same hydroxylated cyanamide **8** from (-)-**5** and (+)-**6**. X-ray analysis of **8** obtained from (+)-β-narcotine ((+)-**6**, 1*S*, 9*S*) revealed 1S,9S-configuration for this "*N*-cyano-1-hydroxy-1,2-seco-narcotine" (**8**)[7]. The authors discuss the stereochemical course of their reactions[6].

We used *Gadamer's* conditions (ECF; $CHCl_3/Et_2O$ 1:1-vol.; 15% KOH)[1] for the cleavage of (-)-α-narcotine (**5**) and obtained a rather stable chlorine containing compound with an urethan- (1695 cm^{-1}) and a five-membered lactone- (1760 cm^{-1}) absorption in its IR-spectrum. The ^{1}H-NMR-spectrum revealed an ethyl increment, the N-CH_3 singlet of the former α-narcotine (**5**) now resonated at lower field strength (cf. Experim. Part). These data are in agreement with structure **9**. - HPLC-analysis (SiO_2; CH_2Cl_2/Et_2O 1:4) showed that the reaction is highly stereoselective producing the diastereomeric urethans **9** in a 93:7 ratio, with $[\alpha]_D^{20}$ = -8° ($CHCl_3$) for the main product (**9**-I). We tried to convert **9**-I into **9**-minor product (**9**-II) under the conditions described in Table 1, but - with the exception of entry 6- **9**-I was recovered with the optical rotation unchanged.



Scheme 3

8



9-I / 9-II (93:7 mixture of diastereomers at C-α)

10

Scheme 4

Table 1: Stereochemical Stability of Urethan **9**-I. Chloro-urethan **9**-I was treated under the conditions cited, the mixtures were analyzed by HPLC (cf. Experim. Part), rotations were measured directly (no work-up*).

Entry	Conditions	Results	Rotation
1	acetone absol.; r.t.	a	b
2	NaI; acetone absol.; r.t.	a	b
3	LiCl; 1,2-dimethoxyethane absol.; r.t.	a	b
4	LiCl + $AlCl_3$; 1,2-dimethoxyethane absol.; r.t.	a	b
5	NaI; 1,2-dimethoxyethane; r.t.	a	b
6	NaI; acetone absol.; reflux	c	d

a: no reaction
b: rotation unchanged
c: formation of stilbene **11**
d: rotation zero (see c)

*) Work-up affords carbinol **10**

Heating the chloro-urethan **9**-I with water or treatment with moist Ag_2O in dioxan produced the hydroxy-urethan **10**. In the meantime *Lee* et al.[8] have prepared this compound by a different procedure and have established its stereochemistry (α*S*,9*S*) by X-ray analysis. Compound **10** is also obtained on prolonged reaction of α-narcotine (**5**) with ECF/KOH in $CHCl_3/Et_2O$. - Treatment of the hydroxy-urethan **10** with $SOCl_2$ regenerated the chloro-urethan **9**-I ($[\alpha]_D^{20}$ = -8° ($CHCl_3$)).

Calculations using the molecular-modelling program SYBYL (TRIPOS) indicate that a decision concerning the stereochemistry of the ECF-cleavage products **9** to be based on ^{1}H-NMR data is scarcely possible: two conformations nearly equal in energy exist for the product of inversion (α-*S*) as well as for the compound produced by retention (α-*R*). Both diastereomers show two energetically favoured conformations, characterized by torsion angles of 52° and 180°, respectively, formed by the H-atoms at C-α and the phthalid-C.

Both diastereomers can adopt conformations with the *meta*-H of the phthalid increment located over the second aromatic group, and according to the ^{1}H-NMR-spectra such an arrangement might exist*).

When **9**-I was heated with 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) the stilbene **11** arose, characterized by the absorption of the enol-lactone at 1775 cm^{-1}, the M^+ at m/z 485 and the cleavage of the stilbene double-bond under EI-conditions [9]. The resonance of the vinylic H at δ = 6.51 ppm points towards *trans*-configuration (increment calculations[10] result in δ (ppm) = 6.13 for *cis*- and 6.33 for *trans*-configuration, respectively).

When (-)-β-narcotine (**6**) (1*R*,9*R*) was treated analogously to α-narcotine (**5**) two chloro-urethans **9**-III and **9**-IV arose in a 1:1 ratio. **9**-III shows $[\alpha]_D^{20}$ = -7.5° ($CHCl_3$); the 100 MHz-^{1}H-NMR-spectrum of chloro-urethan **9**-IV (m.p. 120°C, $[\alpha]_D^{20}$ = +7°) ($CHCl_3$) is identical with the main urethan **9**-I from α-narcotine (**5**) (m.p. 118°C, $[\alpha]_D^{20}$ = -8°) ($CHCl_3$), indicating that **9**-IV and **9**-I are enantiomers.

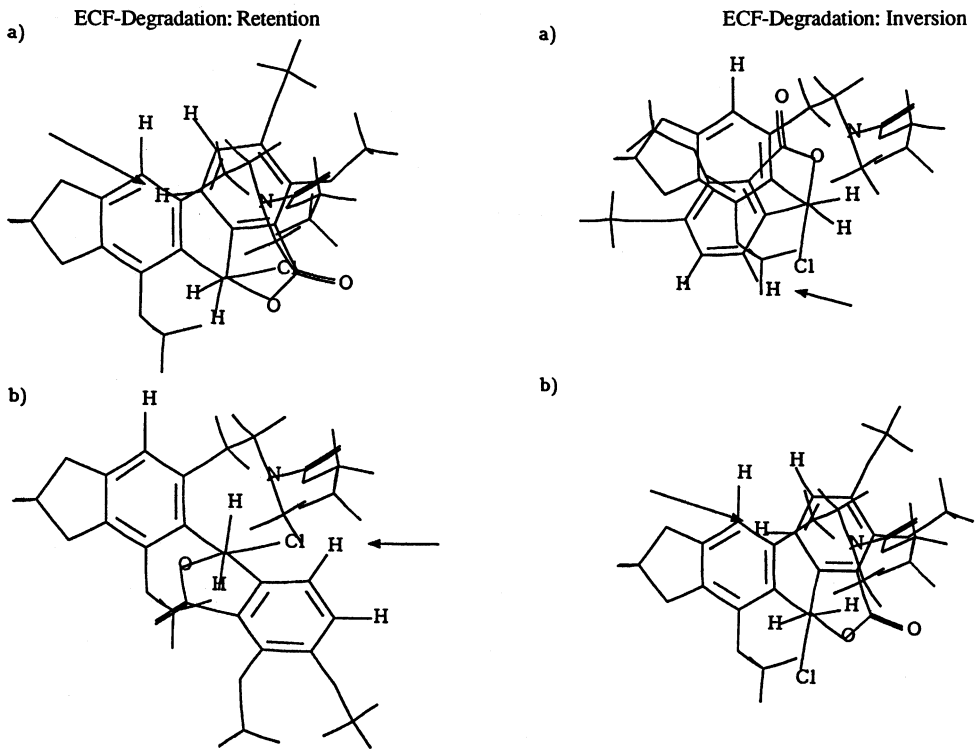
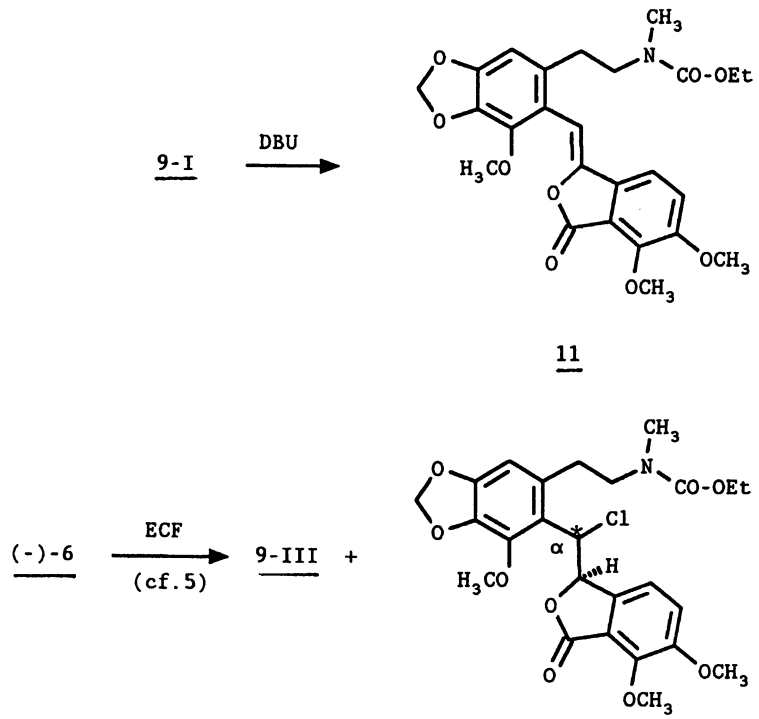
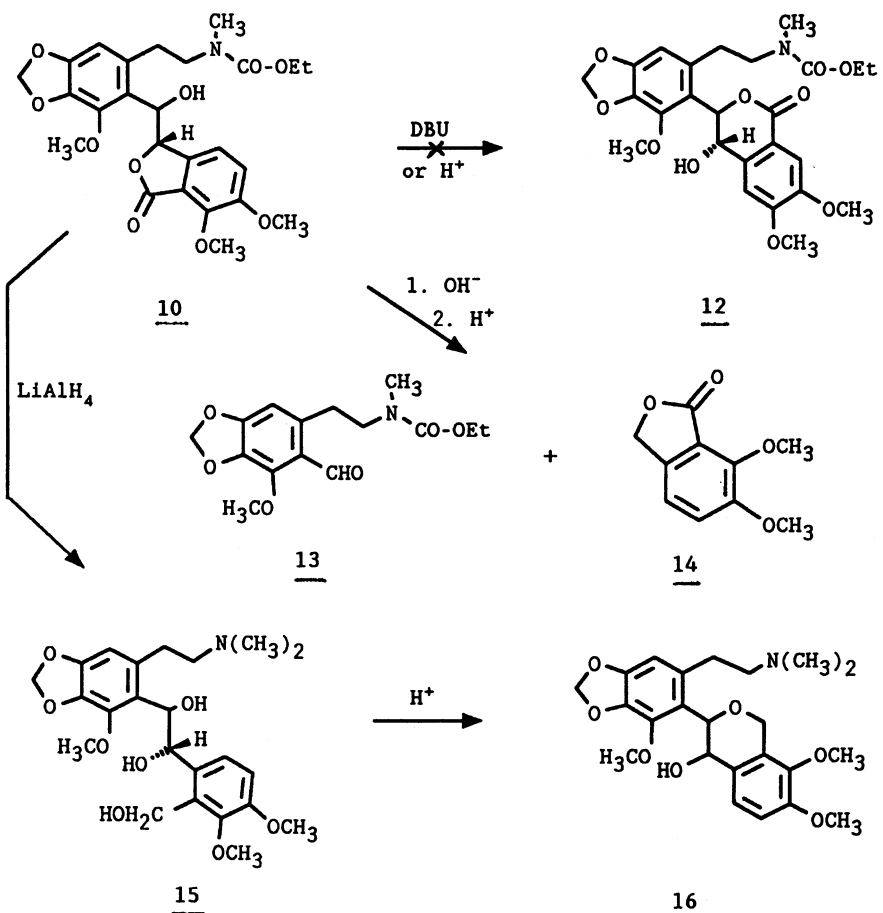


Fig. 1: Energetically favoured conformations a and b for **9**-I following ECF-degradation of **5** either with retention or inversion.

*) The Figures were plotted using ALCHEMY II (TRIPOS) program, the torsion angles were calculated with SYBYL and transfered. The conformations of the side chain and the methoxy groups were not fitted perfectly, because they do not affect the stereochemistry of the centers of chirality.



Scheme 5



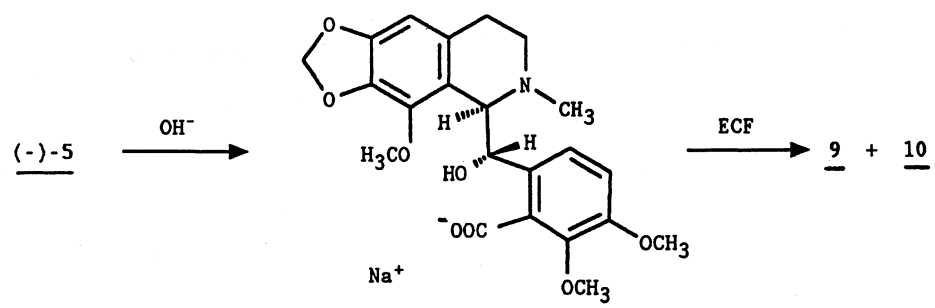
Scheme 6

We tried to convert the 5-ring lactone of **10** into the 6-ring lactone of the 3-phenyl-isochroman-1-one **12** under basic conditions in order to determine the absol. configuration of the carbinol chiral center in **10** (intramolecular transesterification). These experiments failed: compound **10** was split to the aldehyde **13** and to meconine (**14**) because compound **10** is a phenylogous β-hydroxyketone sustaining aldol-cleavage. - When purified **10** was reduced by $LiAlH_4$ to the triol **15**, which is homogenous according to its ^{1}H-NMR-spectrum, followed by H^+-catalyzed ring closure to the 4-hydroxy-3-phenylisochroman **16**, a 3:1 mixture of diastereomers arose. Therefore, this experiment does not indicate the absolute configuration at C-3 in **16** and - consequently - at the carbinol chiral centre of the hydroxy-urethan **10**.

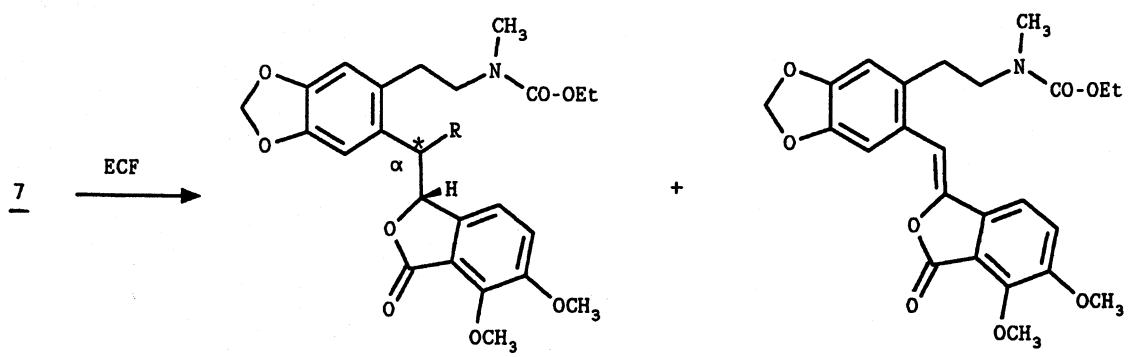
In the course of α-narcotine (**5**)-cleavage a hypothetic quarternary urethan $>N^+(CH_3)$-CO-OEt is converted by external Cl^- to the chloro-urethans, *e.g.* **9** (a quaternary urethan is an intermediate in the ECF-cleavage reaction of C-1-unsubstituted *N*-methyl-1,2,3,4-tetrahydroisoquinolines[11]). This may occur by inversion, retention or *via* a resonance-stabilized carbenium ion, followed by nucleophilic substitution under asymmetric induction exerted by the chiral centre at the lactone group. - In order to have an *intramolecular* nucleophile available, α-narcotine (**5**) was converted to its sodium salt[12], which was treated with ECF/KOH. We isolated a mixture of **9** and **10**. Treatment of this sodium salt in the bomb tube led to **10** (main product) besides some **9**. - ECF is known to activate carboxylate ions by conversion to mixed anhydrides[13]. Probably an analogous reaction regenerated the lactone of α-narcotine (**5**) which is cleaved by ECF (vide supra). When we tried to prevent this lactonization by treatment of the benzylic OH-group in α-narcotine sodium salt with CH_2N_2/BF_3, or dimethyl sulfate under phase transfer conditions[14], or with dihydropyran[15] we obtained α-narcotine (**5**), identical with authentic material. Formation of β-narcotine (**6**) was excluded by the ^{1}H-NMR-spectrum.

Cleavage of (-)-β-hydrastine (7) with ECF

(-)-β-Hydrastine (**7**) was treated with ECF as described for α-narcotine (**5**), leading to two products. One compound reveals an enol-lactone absorption at 1775 cm^{-1} and shows an intensive bluish fluorescence. Its UV-spectrum (λ max = 378 nm) is comparable with that of the analogous compound obtained by *Klötzer*[16] who degraded β-hydrastine (**7**) with phenyl chloroformate/diisopropyl-ethylamine (λ max = 385 nm). Our analytical data (cf. Experim. Part) are in accordance with structure **17**. Because *Klötzer*[16] has confirmed *Z*-configuration for his compound by X-ray analysis, **17** is also a *trans*-stilbene. HPLC-analysis of the mother liquors of **17** indicated a 4:1-mixture of a second compound - [**18**] - with **17**; this mixture could not be separated (*vide infra*). According to *Beilstein's* test and to its MS **18** contains chlorine. M^+ of **18** looses HCl to m/z 455, which



Scheme 7



18: R = Cl

19: R = OCH_3

17

Scheme 8

decomposes to m/z 352 (*McLafferty*). For further fragments cf. Experim. Part. - When we tried to separate **18** from **17** by HPLC, using MeOH/ water 3:1, **18** was converted to the methoxy-analogue **19**.

Contrary to our results, *Whaley*[17] has obtained meconine (**14**) and *N*-carbethoxy-hydrastinine from β-hydrastine (**7**) with ECF, probably due to his more vigorous conditions during work-up. These may have led to an aldol-cleavage analogous to that mentioned with the hydroxy-urethan **10**. - *Olofson* et al.[18], however, obtained an enol lactone, analogous with **17**, when treating **7** with vinyl chloroformate.

Experimental Part

General Remarks: Melting points: Büchi 510 apparatus, uncorrected.- Elemental analyses: Mikroanalytisches Laboratorium, University of Regensburg.- IR-spectra: Beckman Acculab 3; KBr.- ^{1}H-NMR: Varian EM 360 W, Varian EM 390, $CDCl_3$, TMS as internal standard, 60 MHz, if not stated otherwise.- UV-spectra: Uvikon 810, Kontron.- Mass spectra: Varian MAT CH5 und 311A.

ECF-degradation of α*-narcotine* (**5**): *3-{[2-(*β*-N-Ethoxycarbonyl-N-methyl-aminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]-chloro-methyl}-6,7-dimethoxy-1(3H)-isobenzofuranone* (**9**-I)

0.41 g (1 mmole) of α-narcotine (**5**) in 5 ml of $CHCl_3/Et_2O$ were shaken with 5 ml of 15% KOH and 0.8 ml of ethyl chloroformate (ECF) for 2 h at room temp. This procedure was repeated, followed by shaking with 2.5 ml of KOH for 1 h and standing overnight. The combined org. phases were extracted with N HCl, washed with water, dried (Na_2SO_4) and evaporated: oily material, crystallization from Et_2O, recrystallization from benzene/petroleum ether: 0.38 g (74%) of **9**-I, m.p. 118°C, $[\alpha]_D^{20}$ = -8° ($CHCl_3$).- $C_{25}H_{28}ClNO_9$ (521.9) calc. C 57.5 H 5.41 Cl 6.8 found C 57.7 H 5.51 Cl 7.0.

HPLC-analysis: SiO_2; CH_2Cl_2/Et_2O 1:4; Altex apparatus, pump 110 A, detector Kontron 720 LC, 256 nm, integrator Shimadzu C-R1A, sample injector Rheodyne 7125, flow 1.0 ml/min.

Ir (KBr): 1695 (CO), 1760 cm^{-1} (CO).- MS: m/z = 521 (M^+, ^{35}Cl, 2%), 485 (4, *451.49), 418 (3, *335.36), 382 (15, *300.87), 328 (12), 292 (18, *259.95), 264 (2), 225 (3), 220 (100), 205 (12, *191.02), 193 (6), 177 (2), 147 (3), 116 (7).- MS-HR: $C_{12}H_{14}NO_3$ calc. 220.09732 found 220.09726.- ^{1}H-NMR (90 MHz, 50°C): δ (ppm) = 1.25 (t; J = 7.0 Hz, 3H, $-CH_2-CH_3$), 2.56-2.82 (m; 4H, $-CH_2-$), 2.74 (s; 3H, $-NCH_3$), 3.82 (s; 3H, $-OCH_3$), 4.07 (s; 3H, $-OCH_3$), 4.09 (s; 3H, $-OCH_3$), 4.11 (q of d; J_q = 7.0 Hz, J_d = 1.0 Hz, 2H, $-CH_2-CH_3$), 5.00 (d; J = 9.3 Hz, 1H, -CH-Cl), 5.99, 6.03 (AB; J = 1.3 Hz, 2H, $-O-CH_2-O-$), 6.11 (dd; $J_{1,2}$ = 8.4/1.0 Hz, 1H, arom.), 6.28 (d; J = 9.3 Hz, -CH-O-), 6.40 (s; 1H, arom.), 6.92 (d; J = 8.4 Hz, 1H, arom.).- UV (MeOH): λ max (log ε) = 214 (4.58), 292 (sh; 3.60), 309 nm (3.66).

*3-{[2-(*β*-N-Ethoxycarbonyl-N-methyl-aminoethyl)-6-methoxy-4,5-methylenedioxy-phenyl]-hydroxymethyl}-6,7-dimethoxy-1(3H)-isobenzofuranone* (**10**)

a) 0.52 g (1 mmole) of **9**-I were refluxed in 20 ml of water for 5 h. After cooling and extraction with $CHCl_3$, the org. phase was dried (Na_2SO_4) and evaporated: colorless oil, crystals from Et_2O: 0.46 g (91%) of **10**, m.p. 101°C, $[\alpha]_D^{20}$ = -49° ($CHCl_3$).- $C_{25}H_{29}NO_{10}$ (503.5) calc. C 59.6 H 5.81 N 2.8 found C 59.7 H 5.87 N 2.6.- Spectral data are reported by *Lee* et al.[8].

b) 0.52 g (1 mmole) of **9**-I and 1.2 g (5 mmole) of freshly precipitated Ag_2O were refluxed in dioxan for 24 h. Work-up as described and column chromatography (cc) (SiO_2; $CHCl_3/Et_2O$ 1:1) afforded colorless crystals, identical with compound **10** obtained by procedure a).

Reconversion of **10** *to* **9**-I

0.50 g (1 mmole) of **10** in 5 ml of absol. $CHCl_3$ were stirred with 0.14 g (1.2 mmole) of freshly distilled $SOCl_2$ for 2 h at room temp. The mixture was poured into ice water. Extraction ($CHCl_3$), drying (Na_2SO_4), evaporation, cc (SiO_2; $CHCl_3/Et_2O$ 1:1), and crystallization (Et_2O) led to 0.48 g (92%) of **9**-I, m.p. 118°C, $[\alpha]_D^{20}$ = -8° ($CHCl_3$).

Conversion of **9**-I *to stilbene* **11** *(entry 6, Table 1)*

0.10 g (0.2 mmole) of **9**-I in 5 ml of absol. acetone were stirred with 0.30 g (2 mmole) of NaI at reflux temp. under N_2 for 8 h. After dilution with water and extraction ($CHCl_3$) stilbene **11** was obtained, identical with authentic material (see below).

*3-[2-(*β*-N-Ethoxycarbonyl-N-methyl-aminoethyl)-6-methoxy-4,5-methyl-enedioxy-benzylidenyl]-6,7-dimethoxy-1(3H)-isobenzofuranone* (**11**)

0.52 g (1 mmole) of **9**-I and 0.15 g (1 mmole) of DBU in 10 ml of absol. benzene were refluxed for 15 h. After cooling and extraction with 2 N HCl the org. phase was dried (Na_2SO_4) and evaporated: yellow oil; purification by cc (SiO_2; $CHCl_3/Et_2O$ 1:1) produced crystals, recrystallization from benzene: 0.42 g (86%) of **11**, m.p. 170°C.- $C_{25}H_{27}NO_9$ (485.5) calc. C 61.8 H 5.60 found C 61.7 H 5.65.- IR (KBr): 1695 (CO), 1775 cm^{-1} (CO).- MS: m/z = 485 (M^+, 88%), 467 (1, *449.67), 383 (69), 382 (100, *302.45), 369 (26), 341 (19, *315.12), 292 (49), 264 (14, *238.68), 193 (58, *97.51), 189 (10), 116 (97).- ^{1}H-NMR: δ (ppm) = 1.17 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.55-4.10 (m; 6H, $-CH_2-$, $-CH_2-CH_3$), 2.76 (s; 3H, $-NCH_3$), 3.97 (s; 3H, $-OCH_3$), 4.03 (s; 3H, $-OCH_3$), 4.14 (s; 3H, $-OCH_3$), 5.92 (s; 2H, $-O-CH_2-O-$), 6.33 (s; 1H, arom.), 6.51 (s; 1H, vinyl-H), 7.30, 7.60 (AB; J = 9 Hz, 2H, arom.).- UV (MeOH): λ max (log ε) = 220 (4.39), 283 (4.10), 355 nm (4.11).

*ECF-degradation of (-)-*β*-narcotine ((-)-***6***): 3-{[2-(*β*-N-Ethoxycarbonyl-N-methyl-aminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]-chloro-methyl}-6,7-dimethoxy-1-(3H)-isobenzofuranones* (**9**-III *and* **9**-IV)

(-)-**6** was treated with ECF under the conditions used for the ECF-cleavage of (-)-**5**.- **9**-IV was obtained by crystallization from absol. Et_2O, **9**-III by cc (SiO_2; $CHCl_3/Et_2O$ 1:1) and crystallization from Et_2O.

9-III: m.p. 123°C, $[\alpha]_D^{20}$ = -7.5° ($CHCl_3$)

9-IV: m.p. 120°C, $[\alpha]_D^{20}$ = +7° ($CHCl_3$)

DBU-catalyzed cleavage of hydroxy-urethan **10**

0.20 g (0.4 mmole) of **10** and 0.12 g (0.8 mmole) of DBU in 5 ml of absol. dimethylformamide were heated to 120°C for 24 h. After evaporation the residue was suspended in water, the mixture was acidified with 2N HCl and extracted with $CHCl_3$. The org. phase was dried (Na_2SO_4) and evaporated, the remaining oil was purified by cc (SiO_2; $CHCl_3/Et_2O$ 1:1). Meconine (**14**) was obtained from that oil by sublimation (160°C/1 Torr) and crystallized from EtOH/water.- The aldehyde **13** crystallized from Et_2O/water.

14: 0.055 g (71%), m.p. 101°C, lit.[19]: 102°C.- IR (KBr): 1740 cm^{-1} (CO).- MS: m/z = 194 (M^+, 100%), 176 (61, *159.67), 165 (94, *140.34), 163 (16, *136.95), 148 (22, *124.45), 147 (62, *122.78).- ^{1}H-NMR: δ (ppm) = 4.01 (s; 6H, $-OCH_3$), 5.17 (s; 2H, $-CH_2-$), 7.13 (s; 1H, arom.), 7.20 (s; 1H, arom.).

*2-(*β*-N-Ethoxycarbonyl-N-methyl-aminoethyl)-6-methoxy-4,5-methylenedioxybenzaldehyde* (**13**)

Yield 0.04 g (32%), m.p. 103°C, lit.[17]: 104°C.- IR (KBr): 1680 cm^{-1} (CO, CHO).- MS: m/z = 309 (M^+, 3%), 291 (14, *274.05), 263 (2), 236 (6), 206 (80, *137.33), 193 (7), 116 (100).

Cleavage of **10** *with p-toluenesulfonic acid*

0.10 g (0.2 mmole) of **10** and 0.017 (g (0.1 mmole) of *p*-toluenesulfonic acid in 10 ml of absol. CH_2Cl_2 were stirred at room temp. for 48 h. The solution was washed with 5% KOH, the org. phase was dried (Na_2SO_4) and evaporated. From the remaining oil meconine (**14**) was obtained as described above.

2-(2-Hydroxymethyl-3,4-dimethoxyphenyl)-1-[2-(β-N,N-dimethylaminoethyl)-6-methoxy-4,5-methylenedioxylphenyl]-ethan-1,2-diol(**15**)

1.50 g (3 mmole) of **10**, dissolved in 50 ml of absol. THF, were added dropwise to 0.11 g (3 mmole) of $LiAlH_4$ in 5 ml absol. THF at 0°C. After stirring for 3 h excess of $LiAlH_4$ was destroyed by water. A saturated solution of NH_4Cl was added drop by drop under vigorous shaking until the precipitate massed together. The org. phase was decanted, the precipitate was extracted several times with CH_2Cl_2. The org. phases were dried (Na_2SO_4) and evaporated: colorless oil of **15**; 1.20 g (89%), $[\alpha]_D^{20}$ = -69° ($CHCl_3$).- $C_{23}H_{31}NO_8$ (449.4).- IR (KBr): 3400 cm^{-1} (broad; OH).- ^{1}H-NMR: δ (ppm) = 2.13 (s; 6H, $-NCH_3$), 2.20-3.70 (m; 4H, $-CH_2-$), 3.82 (s; 9H, $-OCH_3$), 4.58 (s; 2H, $-CH_2-OH$), 5.07, 5.27 (AB; J = 9 Hz, 2H, $-CH-OH$), 5.85 (s; 2H, $-O-CH_2-O-$), 6.27 (s; 1H, arom.), 6.75, 7.03 (AB; J = 9 Hz, 2H, arom.).- UV (MeOH): λ max (log ε) = 228 (4.39), 283 nm (3.57).

4-Hydroxy-7,8-dimethoxy-3-[2-(β-N,N-dimethyl-aminoethyl)-6-methoxy-4,5-methylenedioxyphenyl]-isochroman(**16**)

0.22 g (0.5 mmole) of **15** were refluxed in 2 N HCl for 2 h. After cooling the solution was adjusted to pH 8.5 by $NaHCO_3$ and extracted with $CHCl_3$. The org. phase was dried (Na_2SO_4) and evaporated. The oily material was purified by cc (Al_2O_3, AcOEt) affording a colorless oil, which slowly crystallized from Et_2O: 0.17 g (79%) of **16**, m.p. 88°C, $[\alpha]_D^{20}$ = +9° ($CHCl_3$).- $C_{23}H_{29}NO_7$ (431.5).- IR (KBr): 3400 cm^{-1} (broad; OH).- MS: m/z = 413 (100%), 368 (12), 337 (7).- ^{1}H-NMR (90 MHz): δ (ppm) = 2.15, 2.22 (2 x s; 6H, $-NCH_3$), 2.28-2.60 (m; 4H, $-CH_2-$), 3.81, 3.83, 3.85, 3.91, 3.96 (5 x s; 9H, $-OCH_3$), 5.14, 5.37 (AB; J = 13.4 Hz, 2H, $-CH_2-O-$), 5.30 (s), 5.79 (s), 5.92 (s; -CH-O-), 5.93, 5.95 (AB; J = 1.4 Hz, 2H, $-O-CH_2-O-$), 6.27, 6.66 (AB; J = 8.3 Hz, arom. H), 6.38, 6.49, 6.55, 6.73, 6.75 (AB, s; arom. H) (all together 3H, arom.).- ^{1}H-NMR (60 MHz, d_6-benzene): δ (ppm) = 2.05; 2.15 (2 x s; 6H, $-NCH_3$), 3.27, 3.33 (2 x s; 3H, $-OCH_3$), 3.55, 3.60 (2 x s; 3H, $-OCH_3$), 3.73, 3.82 (2 x s; 3H, $-OCH_3$).- UV (MeOH): λ max (log ε) = 288 nm (4.00).

ECF-Degradation of α-narcotine Na-salt

0.45 (1 mmole) of **5**-Na-salt[12] were treated with ECF as described for **5** (vide supra).- The oil so obtained was separated by cc (SiO_2; $CHCl_3/Et_2O$ 1:1).
fraction 1: chloro-urethan **9**-I (0.23 g, 44%)
fraction 2: hydroxy-urethan **10** (0.25 g, 50%)

ECF-Degradation of β-hydrastine (**7**): *3-[2-(β-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-methylenedioxy-benzylidenyl]-6,7-dimethoxy-1(3H)-isobenzofuranone* (**17**), *3-{[2-(β-N-Ethoxycarbonyl-N-methyl-aminoethyl)-4,5-methylenedioxyphenyl]-chloromethyl}-6,7-dimethoxy-1(3H)-isobenzofuranone* (**18**), *and 3-{[2-(β-N-Ethoxycarbonyl-N-methylaminoethyl)-4,5-methylene-dioxyphenyl]-methoxymethyl}-6,7-dimethoxy-1(3H)-isobenzofuranone* (**19**)

0.38 g (1 mmole) of **7** were treated with ECF as described for α-narcotine (**5**).- The crystals obtained after usual work-up were suspended in a few ml of Et_2O and filtered: **17**: 0.19 g (42%), m.p. 147-148°C.- $C_{24}H_{25}NO_8$ (455.5) calc. C 63.3 H 5.53 found C 63.5 H 5.43.- IR (KBr): 1690 (CO), 1775 cm^{-1} (CO).- MS: m/z = 455 (M^+, 68%), 352 (100, *272.32), 337 (20), 311 (26), 262 (16), 193 (29), 116 (61).- ^{1}H-NMR: δ (ppm) = 1.27 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.80-4.33 (m; 6H, -CH-, $-CH_2-CH_3$), 2.90 (s; 3H, $-NCH_3$), 3.99 (s; 3H, $-OCH_3$), 4.17 (s; 3H, $-OCH_3$), 6.00 (s; 2H, $-O-CH_2-O-$), 6.72 (s; 1H, vinyl-H), 6.83-7.80 (m; 4H, arom.).- UV (MeOH): λ max (log ε) = 223 (4.33), 242 (sh; 4.26), 305 (4.04), 378 nm (4.18).- Evaporation of the etheral solution (*vide supra*) led to crystals containing stilbene **17** and the chloromethyl derivative **18** (4:1).

18: $C_{24}H_{26}ClNO_8$ (491.9).- IR (KBr): 1680 (CO), 1780 cm^{-1} (CO).- MS: m/z = 491 (M^+, ^{35}Cl, 2%), 455 (37, *421.64), 446 (2), 410 (2), 388 (15), 352 (48, *272.32), 339 (17), 311 (12), 298 (41), 262 (23, *230.35), 193 (43), 116 (100).- MS-HR: $C_{24}H_{26}ClNO_8$: calc. 491.13470 found 491.13579.- ^{1}H-NMR: δ (ppm) = 1.28 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.57-4.00 (m; 5H, $-CH_2-$, -CH-Cl), 2.88 (s; 3H, $-NCH_3$), 3.92 (s; 3H, $-OCH_3$), 4.08 (s; 3H, $-OCH_3$), 4.18 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 5.63 (s; br., 1H, -O-CH-), 5.97 (s; 2H, $-O-CH_2-O-$), 6.60-7.47 (m; 4H, arom.).- UV (MeOH): λ max (qual.) = 219; 242 (sh); 298 nm.

Analytical HPLC (RP 18; MeOH/water 3:1 and Si 60; CH_2Cl_2/Et_2O 4:1) indicated that **18** is converted to the methoxymethyl derivative **19** by MeOH. **19** was isolated by prep. HPLC (RP 18, MeOH/water 3:1): colorless oil.

19: $C_{25}H_{29}NO_9$ (487.5).- IR (film): 1690 (CO), 1760 cm^{-1} (CO).- MS: m/z = 445 (1%), 410 (6), 294 (100), 262 (92, *233.48), 234 (32, *208.99).- ^{1}H-NMR: δ (ppm) = 1.30 (t; J = 7 Hz, 3H, $-CH_2-CH_3$), 2.47-4.00 (m; 5H, $-CH_2-$, -O-CH-), 2.92 (s; 3H, $-NCH_3$), 3.37 (s; 3H, $-CH-OCH_3$), 3.93 (s; 3H, $-OCH_3$), 4.08 (s; 3H, $-OCH_3$), 4.20 (q; J = 7 Hz, 2H, $-CH_2-CH_3$), 5.57 (d; J = 6 Hz, 1H, -O-CH-), 6.02 (s; 2H, $-O-CH_2-O-$), 6.67, 7.22 (AB; J = 9 Hz, 2H, arom.), 6.73 (s; 1H, arom.), 6.83 (s; 1H, arom.).- UV (MeOH): λ max (log ε) = 242 (sh; 3.69), 288 nm (3.26).

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