

Synthesis of the *Preininger*-Alkaloid and its Enantioselective Reduction to Macrostromine

Siavosh Mahboobi and Wolfgang Wiegrebe*

Institute of Pharmacy, University, P.O. Box 397, D 8400-Regensburg, Germany

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The *Preininger*-alkaloid, dehydro-normacrostromine (**2b**, Scheme 1) was synthesized starting from rac. α -acetyl-3,4-dimethoxybenzylcyanide (**3**) (Scheme 2). The key intermediate 4-acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (**11**) is converted via a *Mannich* base to the nitrile **17** (Scheme 7) which in turn is cyclized to the *Preininger*-alkaloid (**2b**) by careful hydrogenation. - Reduction of **2b** with a modified *Iwakuma*-reagent, followed by N-formylation and subsequent LiAlH_4 -reduction produced (*R*)-(+)-macrostromine (enantiomer of **1**) in 72 % optical purity.

Synthese des *Preininger*-Alkaloids und dessen enantioselective Reduktion zu Macrostromin

Das *Preininger*-Alkaloid (Dehydro-normacrostromin, **2b**, Scheme 1) wurde ausgehend von rac. α -Acetyl-3,4-dimethoxybenzylcyanid (**3**) über die Schlüsselverbindung 4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isochinolin (**11**) synthetisiert. Die Umsetzung von **11** über eine *Mannich*-Base zum Nitril **17** (Scheme 7) und dessen schonende Hydrierung führten zum *Preininger*-Alkaloid (**2b**). - Die Reduktion von **2b** mit einem modifizierten *Iwakuma*-Reagenz, N-Formylierung und Alanat-Reduktion lieferten (*R*)-(+)-Macrostromin (Enantiomer von **1**) in 72 proz. optischer Reinheit.

In 1974 *Šantavý, Preininger et al.*¹⁾ reported upon isolation and structure elucidation of a benzylisoquinoline alkaloid from *papaver macrostomum*, *papaveraceae*, named macrostromine (**1**). For this alkaloid *S*-configuration at C-2 of the pyrrolidine-increment was established by chiroptical comparison with (*S*)-(-)-nicotine and (*S*)-(-)-brevicoline.

Traces of a new alkaloid, dehydro-normacrostromine (**2a**) were isolated from *papaver macrostomum* by the same group in 1976²⁾. In commemoration of the late *V. Preininger* we have named dehydro-normacrostromine "*Preininger-alkaloid*". Here we describe the synthesis of this alkaloid and a marginal correction of its structural formula (**2b** instead of **2a**, see below).

Rac. α -acetyl-3,4-dimethoxybenzylcyanide³⁾ (**3**) was converted to **4** which was reduced by B_2H_6 to the β -phenylethylamine **5**. Aminolysis of methyl (3,4-methylenedioxyphenyl)acetate (**6**) with amine **5** afforded the amide **7** which was cyclized to **8** according to *Bischler-Napieralski*⁴⁾. NaBH_4 led to the tetrahydroisoquinoline **9a**. We were not bothered about stereoisomers because the centers of chirality at C-1 and C-4 were abolished in the following steps.

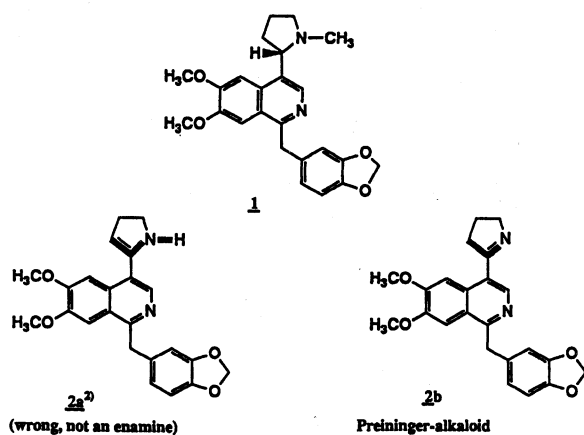
This hydrogenation seems to be a detour because a (dehydrogenated) isoquinoline systems was aspired. On account of the sensitivity of 1-benzyl-3,4-dihydroisoquinoline bases, however, which are easily converted to 1-benzoyl-3,4-dihydroisoquinolines by exposure to air⁵⁾, we could not remove the dithioacetal protecting group successfully. This step, however, would have been mandatory in order to avoid disturbances of the Pd/C-catalyzed dehydrogenation by the sulfur-increment.

Various attempts for cleaving the dithioacetal in **9a** failed⁶⁾. *Meerwein's* reagent⁷⁾, e.g., led to *N*-ethylation (**9b**) but did not attack the dithioacetal.

According to *Fujita*⁸⁾ even those *S*-protecting groups being resistant against $\text{Ti}(\text{NO}_3)_3$ can be removed by $\text{Hg}(\text{ClO}_4)_2$. This reagent has smoothly liberated the ketone moiety of the β -aminoketone **10**. Dehydrogenation of **10** led to the 4-acetyl-1-benzylisoquinoline **11** in 82 % yield besides 6.5 % of **11a**.

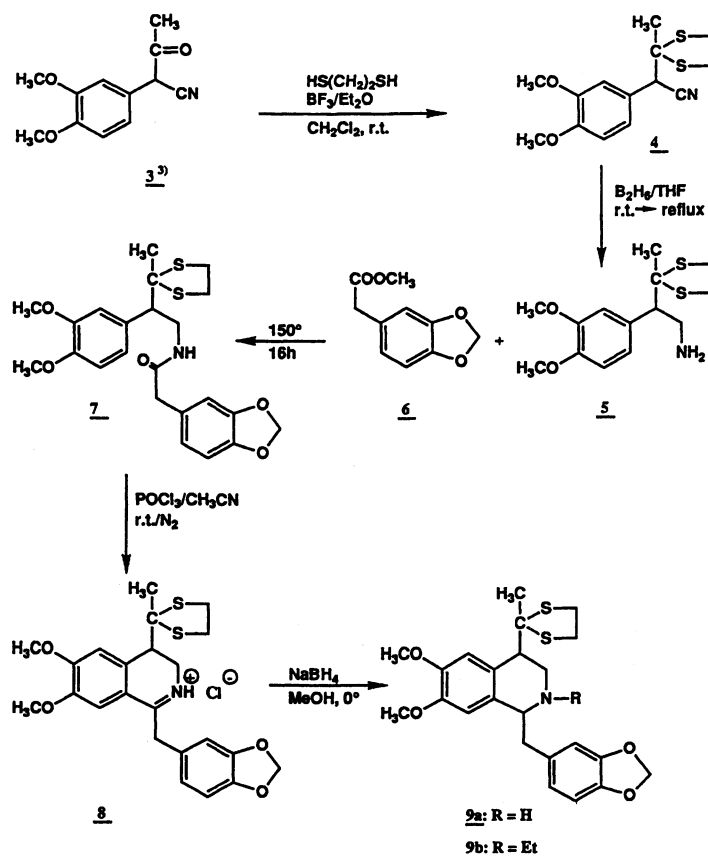
A rationalization for the formation of the by-product **11a** is given in Scheme 4.

Alternatively the dithioacetal moiety in amide **7** was removed by $\text{Hg}(\text{ClO}_4)_2$ producing compound **12** which was cyclized to the 3,4-dihydroisoquinoline **13**, but direct dehydrogenation of **13** afforded the 4-acetyl-1-benzylisoquinoline **11** in 18 - 22 % yield only.

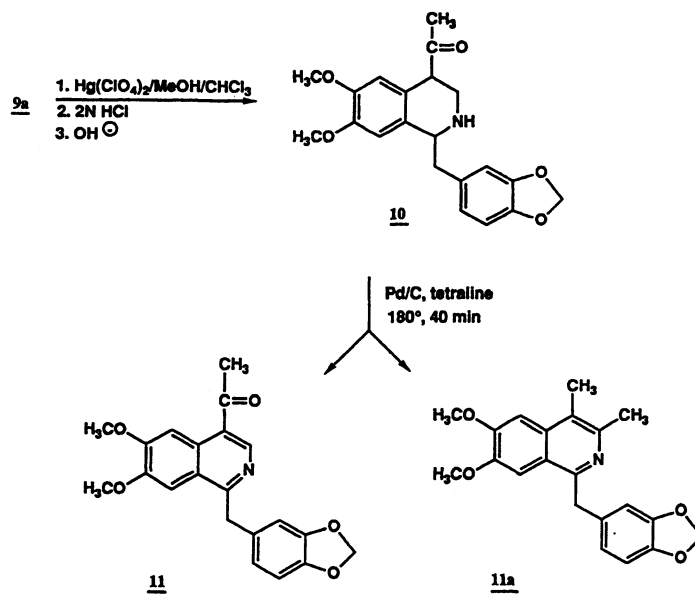


Scheme 1

*) Dedicated to Prof. Dr. K. Bernauer, Basel, on the occasion of his 65th birthday.



Scheme 2

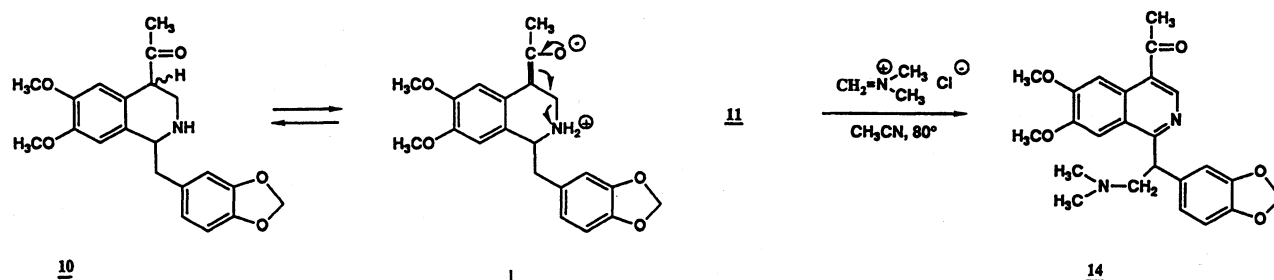


Scheme 3

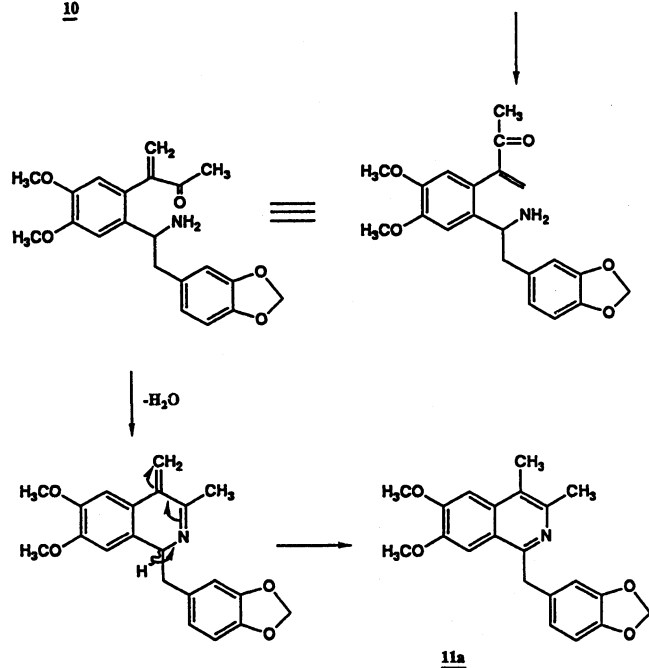
Our efforts to build up the pyrroline moiety of *Preininger*-alkaloid adopting synthetic routes elaborated by *Leete*⁹⁾, *Knott*¹⁰⁾, or *Burckhalter*¹¹⁾ and nicely working in the preparation of 2-(hetero)aryl-pyrrolines¹²⁾ failed: *Böhme* salt (*N,N*-dimethyl-methyleammonium chloride)¹³⁾ or the corresponding acetate¹⁴⁾ did not react with **11** at room

temp., whilst at 80°C (chloride form) or 40°C (acetate form) the CH₂-group was attacked leading to the aza-*Mannich* base **14** (Scheme 6).

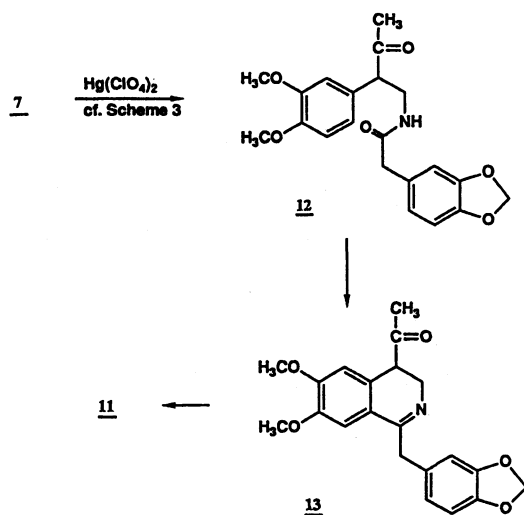
We had been aware of this possibility but 1-(3,4-methylenedioxybenzyl)-6,7-dimethoxyisoquinoline¹⁵⁾ did not react under these conditions. Probably the 4-acetyl increment in **11** increases the C-H-acidity of the CH₂-



Scheme 6



Scheme 4



Scheme 5

group. Therefore, the following steps were performed analogously to those described for our modified synthesis of the nicotiana alkaloid myosmine¹⁶.

^{*)} The enamine/imine tautomerism is generally discussed by *O. Cervinka* in: Enamines, 2nd ed., p. 460, *G.A. Cook*, ed., M. Dekker, Inc., New York ...

Our key compound **11** was silylated according to *Simchen*¹⁷ affording the enol derivative **15**, which was treated with *N,N*-dimethyl-methyleneammonium iodide (*Eschenmoser* salt) followed by hydrolysis with dil. HCl, producing the *Mannich* base **16**; both steps are analogous to those reported by *Danishefsky*¹⁸. **16**-HCl is converted by CN^- to the β -cyanoketone **17**. This step does not work with **16**-base, because it decomposes easily by a retro-*Mannich*-reaction. Careful hydrogenation (cf. Scheme 7) led to **2b**, the *Preininger*-alkaloid.

If the enol derivative **15** is allowed to react with *Böhme-Eschenmoser* salt (iodide form) for 12 h (instead of 90 min only) and the crude mixture is treated with KCN followed by hydrogenation as described above, the C-9-methylated *Preininger*-alkaloid **18** is obtained.

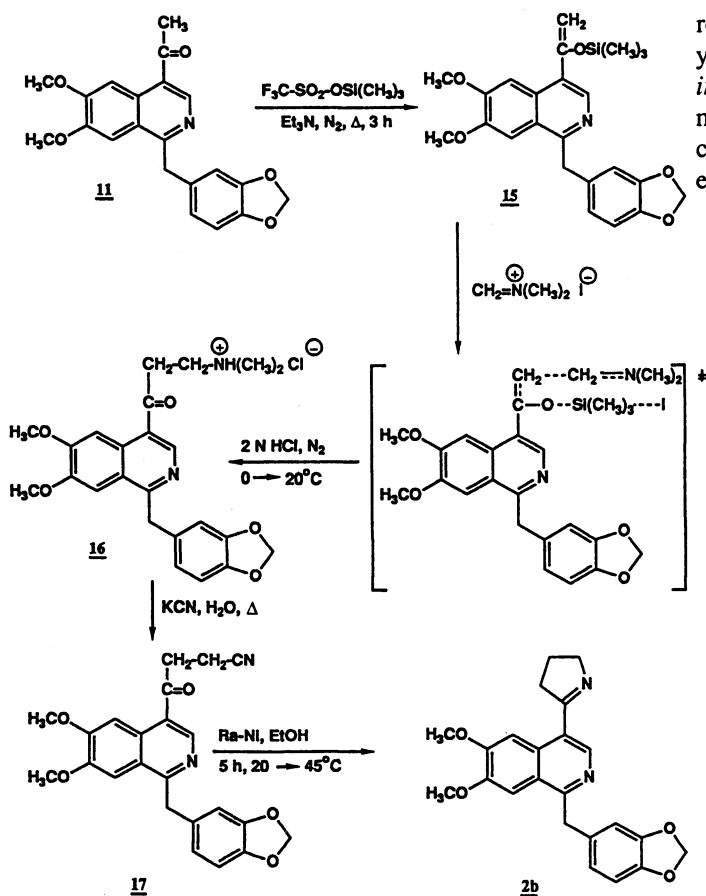
We assume that also in this case the CH_2 -group had reacted with the *N,N*-dimethyl-methyleneammonium salt to an aza-*Mannich* base. Loss of dimethylamine from the pertinent enamine tautomer to the C-9-methylene increment and subsequent hydrogenation then affords compound **18** (cf. Scheme 8).

As mentioned in the introductory remarks formula **2a** had been attributed to dehydro-normacrostromine²⁾, whilst on the other side compound **2b** fits all the analytical data cited by *Šantavý, Preininger et al.*^{2*)}. These authors have deduced the enamine-structure from H/D-exchange experiments with "deuterioethanol", giving rise of an (M+1)-peak in the mass spectrum and "to a smaller extent" of (M+2). Obviously the quantity available (7 mg²⁾) of this alkaloid was too small for ¹H-NMR-experiments at that time. - There are no experimental data for that H/D-exchange experiment. We used CD₃OD and found only 10 % exchange. Because a D⁺-catalyzed reaction is conceivable (traces of CD₃-COOD in the deuterioethanol ?) we have stirred **2b** with CD₃-COOD at 30°C for 3 h. The result (up to 5 H exchanged) is shown in fig. 1.

Obviously not only the aza-allyl system but also the benzylic CH_2 -group is prone to H/D-exchange. - The ¹H-NMR-spectrum of **2b** is shown in fig. 2.

We have reported on the enantioselective hydrosilylation of the *Preininger*-alkaloid (**2b**) affording (*S*)-(-)-macrostromine (**1**) with 33 % ee¹⁹⁾.

Reduction of **2b** with NaBH₄/*N*-benzyloxycarbonyl-L-proline (cf. *Iwakuma*²⁰⁾) and subsequent *N*-formylation by $\text{CH}_3\text{-CO-O-CO-H}$ afforded rotamers of (*R*)-(+)-*N*-formyl-normacrostromine (**19**) which were reduced to (*R*)-(+)-mac-



Scheme 7

rostomine (enantiomer of 1) by LiAlH_4 in 90 % chemical yield and 72 % optical purity (calculated by adopting Preininger's $[\alpha]_D^{25} = 51^\circ (+/- 3^\circ)$, $c = 0.9$, CHCl_3 , for natural macrostomine (1))². Because the reducing reagent for 2b can also be prepared with D-proline this method opens an easy access to natural macrostomine (1) (Scheme 8).

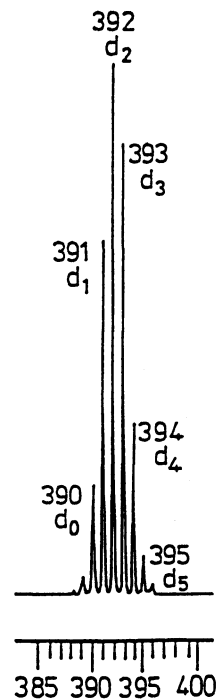
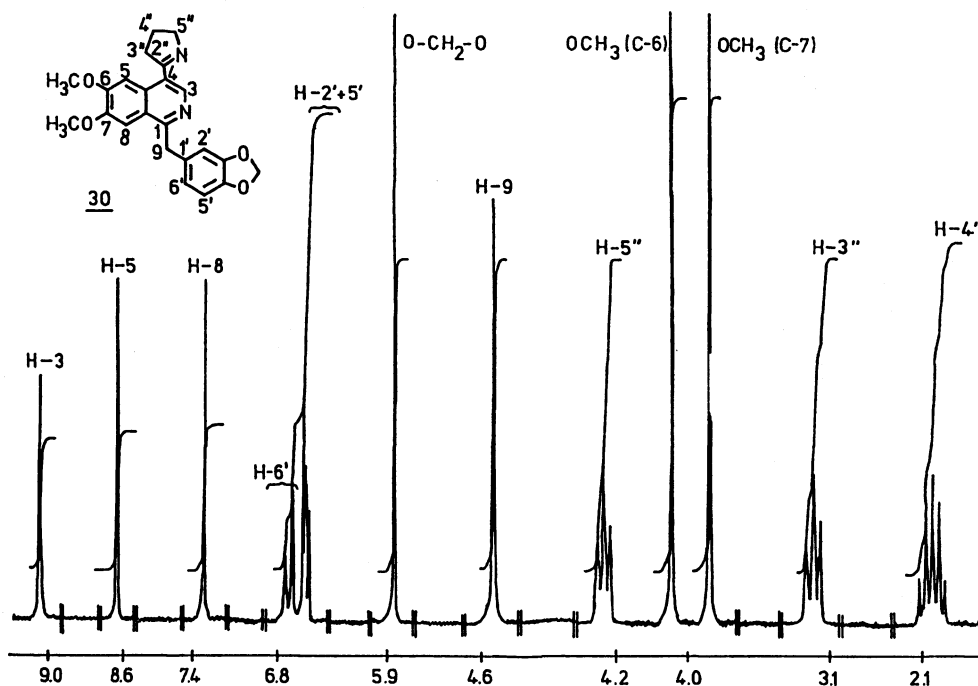
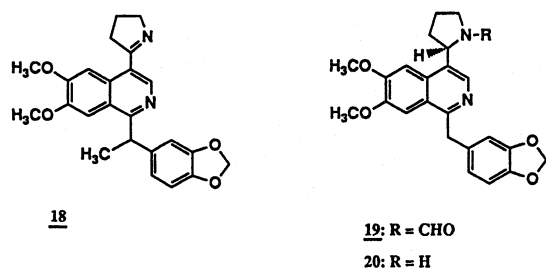


Fig. 1: H/D-exchange; Preininger-alkaloid (2b)

Fig. 2: 400 MHz- $^1\text{H-NMR}$ -spectrum of Preininger-alkaloid (2b)



Scheme 8

Moreover, **19** can be hydrolyzed to the pertinent normacrostromine **20**.

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Experimental Part

General remarks: lit.¹⁶⁾; Al₂O₃: activity II-III, Brockmann. - All temp. in °C.

α -(3,4-Dimethoxyphenyl)- α -(2-methyl-1,3-dithiolan-2-yl)acetonitrile (**4**)

54.8 g (0.25 mole) α -acetyl-3,4-dimethoxybenzylcyanide (**3**)³⁾, dissolved in 400 ml of absol. CH₂Cl₂, 24.54 g (0.26 mole) 1,2-dimercaptoethane and 20 ml BF₃-etherate were stirred at room temp. for 16 h. After addition of water (100 ml) and alkalization with 5 % NaOH the mixture was extracted with CH₂Cl₂. The org. layer was washed with water and dried (Na₂SO₄). After evaporation the light yellow oil was purified by kugelrohr-distillation (210°, 0.05 mm Hg): colourless crystals, m.p. 82 - 83° (MeOH), 70.2 g (95 %). - C₁₄H₁₇NO₂S₂ (295.4) Calcd. C 56.4 H 5.70 N 4.7 Found C 56.3 H 5.66 N 4.6. - UV (MeOH): λ max (log ϵ) = 279 (3.50), 236 nm (3.95). - IR (KBr): 2270 cm⁻¹ (CN). - ¹H-NMR: δ (ppm) = 1.8 (s; 3H, CH₃), 3.2 - 3.48 (m; 4H, S-CH₂-CH₂-S), 3.89 (s; 3H, OCH₃), 3.91 (s; 3H, OCH₃), 4.2 (s; 1H, CH-CN), 6.85 (d; J_{AB} = 9 Hz, 1H, Ar-H-5), 7.5 (dd; J₁₂ = 9/1.5 Hz, 2H, Ar-H-6 and H-2).

2-(3,4-Dimethoxyphenyl)-2-(2-methyl-1,3-dithiolan-2-yl)ethylamine (**5**)

500 ml B₂H₆-tetrahydrofuran complex (1 mole/l) were added drop by drop to 118 g (0.4 mole) of **4** in 350 ml of absol. THF at room temp. under N₂. After 45 min reflux about 750 ml of THF were distilled off and EtOH (130 ml) was added drop by drop at 0°. After alkalization with aqueous NH₃ amine **5** is extracted with CHCl₃. After drying (Na₂SO₄) and evaporation the remaining oil is purified by kugelrohr-distillation (190°, 0.01 mm Hg): nearly colourless viscous oil, 116.2 g (97 %). **5**-base was transformed to **5**-HCl by gaseous HCl in Et₂O: colourless crystals, m.p. 233 - 234°. - C₁₄H₂₂NO₂S₂·Cl (335.9) Calcd. C 50.1 H 6.55 N 4.2 Found C 50.0 H 6.65 N 4.0. - UV (MeOH): λ max (log ϵ) = 275 (3.72), 263 nm (3.71). - IR (KBr): 3200 cm⁻¹ (N-H⁺). - ¹H-NMR: δ (ppm) = 1.04 (s; 2H, NH₂, H/D-exchange), 1.66 (s; 3H, CH₃), 2.84 - 3.6 (m; 3H, Ph-CH-CH₂), 3.26 (s; 4H, S-CH₂-CH₂-S), 3.9 (s; 6H, OCH₃), 6.75 - 7.06 (m; 3H, Ar-H).

N-[2-(3,4-Dimethoxyphenyl)-2-(2-methyl-1,3-dithiolan-2-yl)ethyl]-3,4-methylenedioxyphenylacetamide (**7**)

29.9 g (0.1 mole) amine **5** and 21.3 g (0.11 mole) methyl 3,4-methylenedioxyphenylacetate (**6**) are heated together to 150° for 16 h. After cooling **7** is dissolved in ethyl acetate and filtered. After evaporation, amide **7** is purified by cc (Al₂O₃; EtOAc) and kugelrohr-distillation (230 - 240°, 0.01 mm Hg): colourless crystals, m.p. 108 - 109° (CH₃CN), 42.9 (93 %). - C₂₃H₂₇NO₅S₂ (461.6) Calcd. C 59.8 H 5.89 N 3.0 Found C 59.7 H 5.73 N 3.1. - IR (KBr): 3310 (N-H); 1660 cm⁻¹ (NC=O). - ¹H-NMR: δ (ppm) = 1.61 (s; 3H, CH₃), 2.96 - 4.41 (m; 7H, Ph-CH-CH₂ and S-(CH₂)₂-S), 3.3 (s;

2H, Ph-CH₂), 3.84 (s; 3H, OCH₃), 3.92 (s; 3H, OCH₃), 5.1 - 5.41 (m; 1H, NH, H/D-exchange), 5.94 (s; 2H, O-CH₂-O); 6.28 - 6.91 (m; 6H, Ar-H).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-1-(3,4-methylenedioxybenzyl)-3,4-dihydroisoquinoline-HCl (**8**)

18.46 g (0.04 mole) amide **7** were dissolved in 50 ml of absol. CH₃CN under N₂. 14 ml POCl₃ in 10 ml of absol. CH₃CN were added drop by drop at 0°. The mixture was stirred at room temp. for 4 days, then the crystals were filtered. The filtrate is diluted with acetone (100 ml) and NaHCO₃ (10 ml of a saturated solution) was added: the crystals so obtained were combined with the crystals mentioned above and recrystallized from MeOH: colourless crystals, m.p. 241° (decomp.), 17.3 g (90 %). - C₂₃H₂₆NO₄S₂·Cl (480.0) Calcd. C 57.5 H 5.45 N 2.9 Found C 57.3 H 5.45 N 3.0. - UV (MeOH): λ max (log ϵ) = 305 (sh, 3.78), 286 (4.01), 230 nm (4.43). - IR (KBr): 1670 cm⁻¹ (C=N). - MS: m/z = 443 (M⁺; base, 1 %), 325 (94), 324 (62), 308 (6), 202 (10), 171 (3), 135 (11), 119 (100).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**9a**)

To 14.4 g (0.03 mole) **8**-HCl, dissolved in 130 ml of absol. MeOH, were added under N₂ 2.7 g (71.3 mmole) of NaBH₄ in portions at 0°. The mixture was stirred for 1 h at 0°. Then excess of NaBH₄ was destroyed by 2N HCl, MeOH was distilled off *in vacuo* and the remaining mixture was extracted with CH₂Cl₂. The org. phase is washed with saturated NaHCO₃-solution and dried (Na₂SO₄). Evaporation yielded 13 g of an amorphous powder (97 %). **9**-picrate: m.p. 182 - 183° (EtOH). - C₂₃H₂₇NO₄S₂ (base) (445.6) Calcd. C 51.7 H 4.45 N 8.30 Found C 51.9 H 4.46 N 8.3. - UV (MeOH): λ max (log ϵ) = 285 (3.89), 225 nm (4.16). - IR (KBr): 3400 cm⁻¹ (broad, N-H). - ¹H-NMR: δ (ppm) = 1.85 (s; 3H, CH₃), 1.29 (s; 1H, NH, H/D-exchange), 2.65 - 4.39 (m; 6H, Ph-CH-CH₂ and NH-CH-CH₂), 3.28 (s; 4H, S-(CH₂)₂-S), 3.85 (s; 3H, OCH₃), 3.9 (s; 3H, OCH₃), 5.94 (s; 2H, O-CH₂-O), 6.65 - 6.92 (m; 4H, Ar-H), 7.35 (s; 1H, Ar-H). - MS: m/z = 444 ((M - H)⁺, 1 %), 326 (8), 325 (20), 310 (100), 192 (24), 191 (25), 190 (65), 135 (16), 119 (98).

6,7-Dimethoxy-4-(2-methyl-1,3-dithiolan-2-yl)-N-ethyl-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**9b**)

200 mg (0.45 mmol) of **9a** were dissolved in 5 ml of absol. CH₂Cl₂ and stirred under N₂ with 170 mg (0.9 mmol) of Et₃O·BF₄ in 2 ml of absol. CH₂Cl₂ at 0° for 1 h, then for 4 h at room temp. After alkalization with 2N NaOH the org. layer was separated, washed with water, and dried (Na₂SO₄). The resulting oil is purified by cc (SiO₂; ethyl acetate): light yellow oil, 175 mg (82 %). - C₂₅H₃₁NO₄S₂ (473.7). - ¹H-NMR: δ (ppm) = 1.15 (t; J = 7.4 Hz, 3H, CH₂-CH₃), 1.7 (s; 3H, CH₃), 2.37 - 3.83 (m; 12H, S-(CH₂)₂-S, Ph-CH-CH₂-N-CH-CH₂, and CH₂-CH₃), 3.57 (s; 3H, OCH₃), 3.86 (s; 3H, OCH₃), 5.9 (s; 2H, O-CH₂-O), 6.07 (s; 1H, Ar-H), 6.5 - 6.8 (m; 3H, Ar-H), 7.47 (s; 1H, Ar-H). - MS: m/z = 471 ((M-H)⁺, 3 %), 352 (3), 338 (97), 218 (100), 119 (51).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydroisoquinoline (**10**)

To 7.1 g (16 mmole) dithiolane **9a**, dissolved in 250 ml of CHCl₃ and 50 ml of MeOH, were added 5.28 g Hg(ClO₄)₂ trihydrate in 180 ml of MeOH. After 1 h stirring at room temp. the precipitate was filtered off and the filtrate was basified by 2N Na₂CO₃. After evaporation of the solvents addition of 30 ml of 2N HCl afforded a Hg-containing crystalline precipitate. The pertinent oily base **10** (5.3 g; 90 %) was liberated by 2N NaOH: **10**-HCl: m.p. 185 - 187° (precipitated from Et₂O). - C₂₁H₂₄NO₅·Cl (405.9). Calcd. C 62.1 H 5.96 N 3.5 Found C 62.3 H 5.81 N 3.5. - UV (MeOH): λ max (log ϵ) = 285 (3.85), 231 nm (4.04). - IR (film): 3335 (sharp, N-H); 1710 cm⁻¹ (C=O). - ¹H-NMR: δ (ppm) = 1.82 (s; 1H, NH), 2.15 (s; 3H,

CH₃), 2.65 - 4.28 (m; 6H, Ph-CH-CH₂-N-CH-CH₂-Ph), 3.85 (s; 6H, OCH₃), 5.9 (s; 2H, O-CH₂-O), 6.5 - 6.85 (m; 5H, Ar-H).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline (11) and 6,7-dimethoxy-3,4-dimethyl-1-(3,4-methylenedioxybenzyl)isoquinoline (11a)

3 g (8 mmole) of compound **10** were treated with 500 mg Pd/C 10 % in 8 ml of tetraline at 180° for 40 min. After cooling and filtration the solvent was distilled off *in vacuo*, the residue was dissolved in CH₂Cl₂, the solution was dried over Na₂SO₄ and evaporated. The remaining oil was purified by cc (SiO₂, ethyl acetate): 2.7 g of a mixture of **11** and **11a** which was separated at an analytical scale by HPLC (lichroprepisibo, 30 - 40 nm, 20 bar, 22 ml/min; solvent: CH₂Cl₂/CH₃CN 8 + 2). The CH₂Cl₂ used contains 1 % of the following mixture: 134 ml CH₂Cl₂ + 31 g glacial acetic acid + 35.4 g NEt₃. - Retention time for **11**: 2.8 min, for **11a** 6.2 min.

Preparative yields: 2.4 g (82 %) **11** and 0.183 g (6.5 %) **11a**. The isoquinoline **11** was recrystallized from diisopropylether, m.p. 165 - 166°. **11a** was recrystallized from diisopropyl ether/CH₂Cl₂, m.p. 168 - 169°.

Compound **11**: C₂₁H₁₉NO₅ (365.4) Calcd. C 69.0 H 5.20 N 3.8 Found C 69.1 H 5.37 N 3.6. - UV (MeOH): λ max (log ε) = 335 (3.68), 322 (3.62), 286 (3.89), 240 (sh, 3.96), 226 (sh, 4.70), 214 (4.76). - IR (KBr): 1680 cm⁻¹ (C=O). - ¹H-NMR: δ (ppm) = 2.75 (s; 3H, CH₃), 3.9 (s; 3H, OCH₃), 4.04 (s; 3H, OCH₃), 4.57 (s; 2H, Ph-CH₂), 5.89 (s; 2H, O-CH₂-O), 6.72 (broad s; 3H, Ar-H), 7.39 (s; 1H, H-5), 8.54 (s; 1H, H-8), 9.0 (s; 1H, H-3). - MS: m/z = 365 (M⁺, 76 %), 364 (100), 350 (40), 334 (26), 322 (11), 307 (9), 306 (16), 135 (16).

11a: C₂₁H₂₁NO₄ (351.4) Calcd. C 71.7 H 6.02 N 3.98 Found C 72.3 H 6.18 N 4.18. - ¹H-NMR: δ (ppm) = 2.48 (s; 3H, C-3-CH₃), 2.68 (s; 3H, C-4-CH₃), 3.83 (s; 3H, OCH₃), 3.89 (s; 3H, OCH₃), 4.45 (s; 2H, Ph-CH₂), 5.83 (s; 2H, O-CH₂-O), 6.7 (broad s; 3H, Ar-H), 7.1 (s; 1H, H-5), 7.25 (s; 1H, H-8). - MS: m/z = 351 (M⁺, 58 %), 336 (100), 320 (21), 308 (10), 305 (9), 292 (20), 276 (11), 248 (8), 235 (7), 160 (9).

N-[2-Acetyl-2-(3,4-dimethoxyphenyl)ethyl]-(3,4-methylenedioxyphenyl)-acetamide (12)

To 2.3 g (5 mmole) **7**, dissolved in 100 ml of MeOH and 50 ml of Et₂O, were added drop by drop 2.1 g (5.93 mmole) Hg(ClO₄)₂ trihydrate in 50 ml of MeOH. The suspension was stirred for 1 h at room temp. The precipitate was filtered off, washed with CH₂Cl₂ and discarded. The combined org. phases were washed with 30 ml of 2N NaOH and with saturated NaCl-solution. After drying (Na₂SO₄) and evaporation, compound **12** was purified by cc (Al₂O₃; CH₂Cl₂/CH₃N 9 + 1) and kugelrohr-distillation (200°, 0.05 mm Hg): colourless crystals, mp. 117 - 118°, 1.8 g (93 %). - C₂₁H₂₃NO₆ (385.4) Calcd. C 65.4 H 6.01 N 3.6 Found C 65.2 H 6.18 N 3.7. - UV (MeOH): λ max (log ε) = 283 (3.81), 235 nm (4.00). - IR (KBr): 3330 (sharp, N-H); 1720 (C=O); 1655 cm⁻¹ (NC=O). - ¹H-NMR: δ (ppm) = 2.02 (s; 3H, CH₃), 3.3 - 4.3 (m; 3H, Ph-CH-CH₂-N), 3.39 (s; 2H, NCO-CH₂-Ph), 3.81 (s; 3H, OCH₃), 3.84 (s; 3H, OCH₃), 5.7 - 6.03 (m; 1H, NH), 5.92 (s; 2H, O-CH₂-O), 6.49-6.92 (m; 6H, Ar-H).

4-Acetyl-6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-3,4-dihydroisoquinoline (13) and its dehydrogenation to 11

1.3 g (3.4 mmole) **12** were heated under reflux for 4 h with 3 ml of POCl₃ in 30 ml of absol. CH₃CN under N₂. The solvent was evaporated, the residue was dissolved in ice/water and basified with Na₂CO₃ under N₂. Extraction with Et₂O, drying of the org. phase (Na₂SO₄) and evaporation *in vacuo* afforded the dihydroisoquinoline **13**, which was dissolved in 10 ml of tetraline and dehydrogenated by heating this solution to 190 - 200° with 300 mg Pd/C 10 % for 3 h. Then the solvent was distilled off, the residue was suspended in CH₂Cl₂ and the catalyst was removed by filtration. The org. phase was dried (Na₂SO₄) and evaporated. The oily residue was purified by cc (SiO₂; ethyl acetate). - Yield (both steps): 250 mg (20 %) **11**.

4-Acetyl-6,7-dimethoxy-9-(N,N-dimethylaminomethyl)-1-(3,4-methylenedioxybenzyl)isoquinoline (14)

28 mg (0.3 mmole) N,N-dimethyl-methyleneammoniumchloride and 100 mg (0.27 mmole) **11** in 3 ml of absol. CH₃CN were heated to 80° for 3 h. After evaporation of the solvent *in vacuo* the residue was treated with 2N Na₂CO₃-solution and extracted with CH₂Cl₂. Drying (Na₂SO₄) and evaporation *in vacuo* afforded an oil which was purified by cc (SiO₂; MeOH): light yellow crystals, m.p. 138 - 141° (Et₂O/hexane), yield 90 mg (71 %). - C₂₄H₂₆N₂O₅ (422.5). - UV (MeOH): λ max (log ε) = 333 (3.87), 291 (3.81), 251 (sh, 4.46), 235 nm (4.51). - IR (KBr): 1690 cm⁻¹ (C=O). - ¹H-NMR (400 MHz): δ (ppm) = 2.35 (s; 6H, N(CH₃)₂), 2.76 (s; 3H, COCH₃); 3.03 - 3.08 (AA'B, dd, J_{1/2} = 12.4/6.95 Hz, 1H, Ph-CH-CH₂), 3.64 - 3.77 (AA'B, dd, J_{1/2} = 12.4/6.95 Hz, 1H, Ph-CH-CH₂), 3.98 (s; 3H, OCH₃), 4.02 (s; 3H, OCH₃), 5.0 - 5.15 (m; 1H, Ph-CH₂-CH₂), 5.85 (d, J = 1.4 Hz, 1H, O-CH₂-O), 5.88 (d; J = 1.4 Hz, 1H, O-CH₂-O), 6.69 - 6.90 (m; 3H, Ar-H), 7.51 (s; 1H, Ar-H), 8.50 (s; 1H, Ar-H), 9.04 (s; 1H, H-3). - MS: m/z = 422 (M⁺, 6 %), 389 (25), 307 (100), 292 (98).

3-Cyano-1-[6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinolin-4-yl]-propan-1-one (17)

3.65 g (10 mmole) **11** were dissolved in 70 ml of absol. benzene under N₂ and stirred with 1.2 g Et₃N and 2.16 ml of F₃C-SO₂-O-Si(CH₃)₃ at 0° for 30 min and for 3 h at reflux temp. After cooling the benzene phase was separated and evaporated; viscous orange oil of **15** (4.4 g) which was not purified but directly dissolved in 30 ml of absol. CH₂Cl₂ under N₂ at 0° and stirred with 2 g of N,N-dimethyl-methyleneammonium iodide first at 0° for 1 h than for 3 h at room temp.. After evaporation of CH₂Cl₂ the colourless oil was dissolved in 12 ml of 2N HCl at 0° under N₂, then the solution was stirred for 2 h at room temp. After evaporation the Mannich base **16**-HCl was obtained (colourless oil). - This oil and 0.7 g KCN were dissolved in 80 ml of water of 90° and refluxed for 2 h under N₂. After cooling extraction with CH₂Cl₂, drying (Na₂SO₄), and evaporation led to the nitrile **17** which was purified by cc (Al₂O₃; CHCl₃): colourless crystals from EtOH, m.p. 172 - 173°, total yield (4 steps): 2.06 g (51 %). - C₂₃H₂₀N₂O₅ (404.4) Calcd. C 68.3 H 4.98 N 6.6 Found C 68.2 H 4.98 N 6.6. - UV (MeOH): λ max (log ε) = 333 (3.88), 291 (3.81), 246 (sh, 4.47), 231 nm (4.54). - IR (KBr): 2260 (C≡N); 1675 cm⁻¹ (C=O). - ¹H-NMR: δ (ppm) = 2.87 (t; J = 7.5 Hz, 2H, CH₂-CH₂CN), 3.56 (t; J = 7.5 Hz, 2H, CH₂-CH₂-CN), 3.94 (s; 3H, OCH₃), 4.08 (s; 3H, OCH₃), 4.58 (s; 2H, Ar-CH₂-Ph), 5.9 (s; 2H, O-CH₂-O), 6.69 - 6.8 (m; 3H, Ar-H), 7.4 (s; 1H, Ar-H-5), 8.54 (s; 1H, Ar-H-8), 9.0 (s; 2H, Ar-H-3). - MS: m/z = 404 (M⁺, 80 %), 403 (100), 389 (35), 373 (23).

6,7-Dimethoxy-1-(3,4-methylenedioxybenzyl)-4-(1-pyrrolin-2-yl)isoquinoline (2b), Preininger-alkaloid

600 mg (1.5 mmole) **17**, dissolved in 100 ml of absol. EtOH, were heated to 40 - 45° for 5 h with 2 g Raney-Ni in 6 ml of absol. EtOH, previously saturated with NH₃ at 0°. Efficient cooling in order to prevent escaping of NH₃ is mandatory. In addition the reflux condenser has to be closed by a stopper plug. After cooling the catalyst was filtered off and the solvent was evaporated *in vacuo*. **2b** is purified by cc (Al₂O₃; CHCl₃): colourless crystals from acetone, m.p. 192 - 193° (lit. 193° - 195°²⁾, 540 mg (92 %). - UV (EtOH): λ max (log ε) = 332 (sh, 3.45), 317 (3.47), 293 (3.52), 247 nm (4.26). - UV (EtOH + HCl): λ max (log ε) = 340 (3.95), 262 (4.49), 235 nm (4.44). - IR (KBr): 1620 cm⁻¹ (C=N). - ¹H-NMR: δ (ppm) = 2.02 - 2.10 (m; 2H, pyrrol-H-4''), 3.12 - 3.16 (m; 2H, pyrrol-H-3''), 3.92 (s; 3H, OCH₃ (C-7)), 4.03 (s; 3H, OCH₃ (C-6)), 4.21 - 4.25 (m; 2H, pyrrol-5''-H), 4.56 (s; 2H, Ph-CH₂), 5.88 (s; 2H, O-CH₂-O), 6.7 - 6.72 (m; 2H, H-2' and H-5'), 6.77 (dd; J_o = 7 Hz, J_m = 1 Hz, H-6'), 7.37 (s; 1H, H-8), 8.61 (s; 1H, H-5), 9.02 (s; 1H, H-3). - MS: m/z = 390 (M⁺, 99 %), 389 (100), 375 (49), 359 (19), 135 (24).

