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

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The *Preininger*-alkaloid, dehydro-normacrostomine (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-methylene-dioxybenzyl)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 LiAlH₄-reduction produced (*R*)-(+)-macrostomine (enantiomer of 1) in 72 % optical purity.

In 1974 Šantavý, Preininger et al.¹⁾ reported upon isolation and structure elucidation of a benzylisoquinoline alkaloid from papaver macrostomum, papaveraceae, named macrostomine (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-normacrostomine (2a) were isolated from *papaver macrostomum* by the same group in 1976²⁾. In commemoration of the late V. *Preininger* we have named dehydro-normacrostomine "*Preininger-alkaloid*". Here we describe the synthesis of this alkaloid and a marginal correction of its structural formula (2b instead of 2a, see below).



Scheme 1

Synthese des Preininger-Alkaloids und dessen enantioselektive Reduktion zu Macrostomin

Das Preininger-Alkaloid (Dehydro-normacrostomin, 2b, Scheme 1) wurde ausgehend von rac. α -Acetyl-3,4-dimethoxybenzylcyanid (3) über die Schlüsselverbindung 4-Acetyl-6,7-dimethoxy-1-(3,4-methylendioxybenzyl)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)-(+)-Macrostomin (Enantiomer von 1) in 72 proz. optischer Reinheit.

Rac. α -acetyl-3,4-dimethoxybenzylcyanide ³⁾ (3) was converted to 4 which was reduced by B₂H₆ to the β -phenylethylamine 5. Aminolysis of methyl (3,4-methylenedioxyphenyl)acetate (6) with amine 5 afforded the amide 7 which was cylcized to 8 according to *Bischler-Napieralski* ⁴⁾. NaBH₄ 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 air ⁵¹, we could not remove the dithioketal 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 dithioketal in 9a failed ⁶⁾. Meerwein's reagent ⁷⁾, e.g., led to N-ethylation (9b) but did not attack the dithioketal.

According to Fujita⁸⁾ even those S-protecting groups being resistant against Tl(NO₃)₃ can be removed by Hg(ClO₄)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 dithioketal moiety in amide 7 was removed by $Hg(ClO_4)_2$ 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.

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



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-methyleneammonium 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-dimethoxyisoquinoline $^{15)}$ did not react under these conditions. Probably the 4-acetyl increment in 11 increases the C-H-acidity of the CH₂-



Scheme 5

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



Our key compound 11 was silvlated according to Simchen¹⁷⁾ 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 16base, 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 tautomere to the C-9-methylene increment und subsequent hydrogenation then affords compound 18 (cf. Scheme 8).

As mentioned in the introductory remarks formula 2a had been attributed to dehydro-normacrostomine ²⁾, whilst on the other side compound 2b fits all the analytical data cited by *Šantav'*, *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 mg ²⁾) 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 CH₂-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)-(-)-macrostomine (1) with 33 % ee ¹⁹.

Reduction of **2b** with NaBH₄/N-benzyloxycarbonyl-Lproline (cf. *Iwakuma*²⁰⁾) and subsequent *N*-formylation by CH₃-CO-O-CO-H afforded rotamers of (R)-(+)-*N*-formylnormacrostomine (**19**) which were reduced to (R)-(+)-mac-

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



Scheme 7

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



Fig. 2: 400 MHz-¹H-NMR-spectrum of Preininger-alkaloid (2b)



Moreover, **19** can be hydrolyzed to the pertinent normacrostomine **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; J_{1/2} = 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-methylenedioxyphenyl)acetamide (7)

29.9 g (0.1 mole) amine 5 and 21.3 g (0.11 mole) methyl (3,4-methylenedioxyphenyl)acetate (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-methylendioxybenzyl)-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-C<u>H-CH₂</u>), 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)-1,2,3,4tetrahydroisoquinoline (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 CH_2Cl_2 , the solution was dried over Na_2SO_4 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 (lichroprepsibo, 30 - 40 nm, 20 bar, 22 ml/min; solvent: $CH_2Cl_2/CH_3CN 8 + 2$). The CH_2Cl_2 used contains 1 % of the following mixture: 134 ml $CH_2Cl_2 + 31$ 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: $C_{21}H_{19}NO_5$ (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: $C_{21}H_{21}NO_4$ (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 war 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-(3,4methylenedioxybenzyl)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), 2.91 (3.81), 251 (sh, 4.46), 2.35 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), 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-4yl]-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): $\lambda \max (\log \epsilon) = 332$ (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, pyrr.-H-4"), 3.12 - 3.16 (m; 2H, pyrr.-H-3"), 3.92 (s; 3H, OCH₃ (C-7)), 4.03 (s; 3H, OCH3 (C-6)), 4.21 - 4.25 (m; 2H, pyrr.-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; $J_0 = 7 Hz$, $J_m = 1 Hz$, 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).

6,7-Dimethoxy-9-methyl-1-(3,4-methylenedioxybenzyl)-4-(1-pyrrolin-2-yl)-isoquinoline (18)

Compound **18** is formed, if the silylated enol derivative **15** reacts for 12 h with N,N-dimethyl-methyleneammonium iodide. For the following steps, leading to nitril **17**, the mixture was not separated. Compound **18** is easily separated from *Preininger*-alkaloid (**2b**) by cc (SiO₂; CH₂Cl₂/CH₃CN 8 + 2) and recrystallization from EtOH: colourless crystals m.p. 142.5 - 143⁺, 7 - 9 % yield. - C₂₄H₂₄N₂O₄ (404.5) Calcd. C 71.3 H 5.98 N 6.9 Found C 71.4 H 6.11 N 6.8. - UV (EtOH): λ max (log ε) = 328 (sh, 3.87), 314 (3.89), 292 (3.94), 246 nm (4.52). - IR (KBr): 1625 cm⁻¹ (C=N). - ¹H-NMR: δ (ppm) = 1.84 (d; J = 6 Hz, 3H, Ph-CH-CH₃), 1.85 - 2.25 (m; 2H, pyrr.-H-4), 2.98 - 3.31 (m; 2H, pyrr.-H-3), 3.90 (s; 3H, OCH₃), 4.1 (s; 3H, OCH₃), 4.1 - 4.37 (m; 2H, pyrr.-H-5), 4.89 (q; J = 6 Hz, 1H, Ph-CH-CH₃), 5.84 (s; 2H, O-CH₂-O), 6.63 - 6.93 (m; 3H, Ar-H), 7.44 (s; 1H, Ar-H), 8.75 (s; 1H, Ar-H), 9.16 (s; 1H, H-3). - MS: m/z = 404 (M⁺⁺, 100 %), 403 (86), 389 (35), 373 (8), 149 (8), 135 (12).

(R)-(+)-N-Formylnormacrostomine (19)

The reducing reagent was prepared by adding 750 mg of L-Z-proline to 35 mg of NaBH₄ in 5 ml absol. THF. This mixture was stirred for 1 h at 0° and 3 h at room temp.. After evaporation of THF the reducing complex is used as such. - 70 mg (0.18 mmole) **2b**, dissolved in 4 ml of absol. CH₂Cl₂, were added to the proline-complex mentioned above; the mixture was stirred for 2 h at 0° and 60 h at room temp.. After evaporation the residue was dissolved in 2 ml of H-CO-O-CO-CH₃ at 0° and stirred for 15 min at 0° and 15 min at room temp.. After 40 min heating at 70° excessive anhydride was distilled off *in vacuo*. The residue was dissolved in CH₂Cl₂, the solution was dried (Na₂SO₄) and evaporated, the remaining oil was purified by cc (Al₂O₃, CHCl₃): colourless crystals, m.p. 140°. - IR- and mass-spectrum are identical with those reported for the (S)-(-)-enantiomer ²⁰⁾. - Optical rotation: (+), qual.

(R)-(+)-normacrostomine (20)

17 mg (0.04 mmole) **19** were heated to reflux in 2.5 ml of 3N HCl for 2.5 h. After cooling and neutralization with NaHCO₃ **20** was extracted with CH₂Cl₂. The org. phase was dried (Na₂SO₄) and evaporated: 13 mg (84 %) light yellow amorphous powder. - C₂₃H₂₄N₂O₄ (392.5). - UV (MeOH, qual.): λ max = 329; 315; 284; 245 (sh); 240 nm. - IR (KBr): 3400 cm⁻¹ (N-H, broad). - ¹H-NMR (250 MHz): δ (ppm) = 1.85 - 4.71 (m; 8H, CH-(CH₂)₃-NH: pyrr.-H), 3.89 (s; 3H, OCH₃), 4.02 (s; 3H, OCH₃), 4.46 (s; 2H, Ph-CH₂), 5.86 (s; 2H, O-CH₂-O), 6.68 - 6.76 (m; 3H, Ar-H), 7.31 (s; 1H, Ar-H), 7.46 (s; 1H, Ar-H), 8.46 (s; 1H, Ar-H-3). - MS (12 eV): m/z = 392 (M⁺⁻¹, 100 %). - Optical rotation: (+), qual.

(R)-(+)-macrostomine ((+)-1)

50 mg (0.12 mmole) 19, dissolved in 4 ml of absol. THF, were added drop by drop under N_2 to 70 mg LiAlH₄ in 5 ml of absol. THF at 0°C. This mixture was stirred for 15 min at 0°, 15 min at room temp. and 40 min under reflux. After cooling to 0°, excessive LiAlH₄ was destroyed by as

little as possible water and the mixture was extracted with Et₂O (3 x 10 ml) and 10 ml of CH₂Cl₂. The combined org. phases were dried (Na₂SO₄) and evaporated. (+)-1 was purified by cc (Al₂O₃; CH₂Cl₂/CH₃CN 9 + 1): light yellow powder, 44 mg (90 %). - m.p. 95 - 100°C (lit. ²⁾: 107 - 110° for optically pure (-)-1). - $[\alpha]_D^{25} = 37^*$ (c = 0.9, CHCl₃; lit. ²⁾: 51°): optical purity = 72 %. - ¹H-NMR (400 MHz): δ (ppm) = 1.9 - 2.08 (m; 3H, H-3'', H-4'', H-5''), 2.25 (s; 3H, N-CH₃), 2.29 - 2.37 (m; 2H, H-3'', H-4''), 3.28 - 3.33 (m; 1H, H-5''), 3.5 - 3.56 (m; 1H, H-2''), 3.89 (s; 3H, OCH₃), 3.99 (s; 3H, OCH₃), 4.49 (s; 2H, Ph-CH₂), 5.87 (s; 2H, O-CH₂-O), 6.7 - 6.72 (m; 1H, H-6'), 6.77 - 6.79 (m; 2H, H-2' and H-5'), 7.32 (s; 1H, H-8), 7.79 (s; 1H, H-5), 8.40 (s; 1H, H-3).

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