Removal of the Pyrrolidine Group by Dehydrogenation of a 4-Pyrrolidin-2-yl-tetrahydroisoquinoline+)

Siavosh Mahboobi, Engelbert Seidl, Ernst Eibler, and Wolfgang Wiegrebe

Institute of Pharmacy, University, P. O. Box 101042, W-8400 Regensburg, Germany

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Dehydrogenation of 6,7-dimethoxy-1-methyl-4-(*N*-methyl-pyrrolidin-2-yl)-3,4-dihydroisoquinoline (**9**) by Pd/C in tetraline leads to dehydrogenated products, rearrangement, and elimination of the pyrrolidine group mainly as *N*-methylpyrrolidine (Scheme 3).

Abspaltung der Pyrrolidin-Gruppe bei der Dehydrierung eines 4-(Pyrrolidin-2-yl)-tetrahydroisochinolins

Die Dehydrierung von 6,7-Dimethoxy-1-methyl-4-(*N*-methyl-pyrrolidin-2-yl)-3,4-dihydroisochinolin (**9**) mit Pd/C in Tetralin führt zu dehydrierten Produkten, zur Umlagerung und zur Abspaltung der Pyrrolidingruppe hauptsächlich als *N*-Methylpyrrolidin (Schema 3).

The last step of our synthesis of rac. macrostomine comprises dehydrogenation of the pertinent 3,4-dihydroisoquinoline increment in **2** by Pd/C in tetraline at 205-210 °C. Under these conditions **2** is converted to rac. macrostomine (**1**) and mainly to the 1-benzylisoquinoline **3**[1].

Sharma and *Kapil*[2] prepared compound **2** by a different route. They quote that a "complex mixture" was obtained by Pd/C-dehydrogenation of **2**, from which **1** was isolated in 20% yield, whilst *Wykypiel* and *Seebach*[3] when dehydrogenating a 1,2-dibenzyl-4-(*N*-formylpyrrolidin-2-yl)-tetrahydroisoquinolin-4-ol observed elimination of the benzyl group from C-1 as a side reaction besides aromatization (note 13 in lit.[3]).

An analogous cleavage reaction was observed by *Winterfeldt* et al.[4] when they tried to dehydrogenate a 4-(1-methyl-pyrrolidin-2-yl)-3,4-dihydro-9*H*-pyrido[3,4-*b*]indole with various oxidative reagents to the pertinent harman derivative.

In order to get some insight into the fate of the pyrrolidine increment the volatile components of the dehydrogenation of **2** to **1** were analyzed by GC-MS: we found *N*-methylpyrroline and traces of *N*-methylpyrrolidine[5]. However, these compounds are hydrogenated and dehydrogenated under these conditions so that no clear-cut view of the cleavage mechanism could be obtained[5].

Here we describe dehydrogenation of a 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, substituted at C-4 with pyrrolidine or pyrroline increments (compounds **8** and **9**).

+) Dedicated to Prof. *Fleischhacker*, Wien, on the occasion of his 60th birthday.

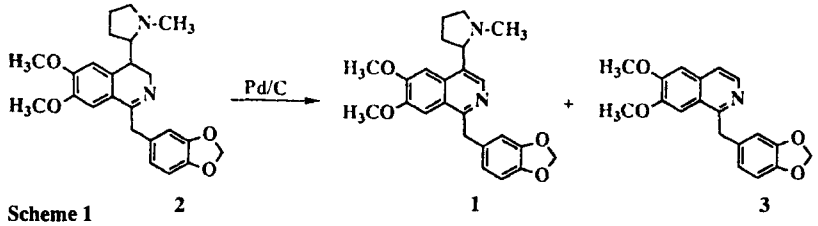
Synthesis

2-(3,4-Dimethoxyphenyl)-2-(*N*-methylpyrrol-2-yl)-ethylamine (**4**), prepared according to *Kapil*[2] by enamine addition of *N*-methylpyrrol to the pertinent ω-nitrostyrene and hydrogenation of the nitro-group to **4** over Raney-Ni, was converted to the acetamide **5**. At this stage the pyrrol ring was hydrogenated to the corresponding 2,5-dihydro-derivative **6** by Zn/HCl/MeOH, which, in turn, was fully hydrogenated to **7** by H_2/Pd/$BaSO_4$ in AcOEt. *Bischler-Napieralski* ring closure of the pyrroline **6** led to **8**, that of **7** to the pyrrolidine-substituted 3,4-dihydroisoquinoline **9**.

Dehydrogenations

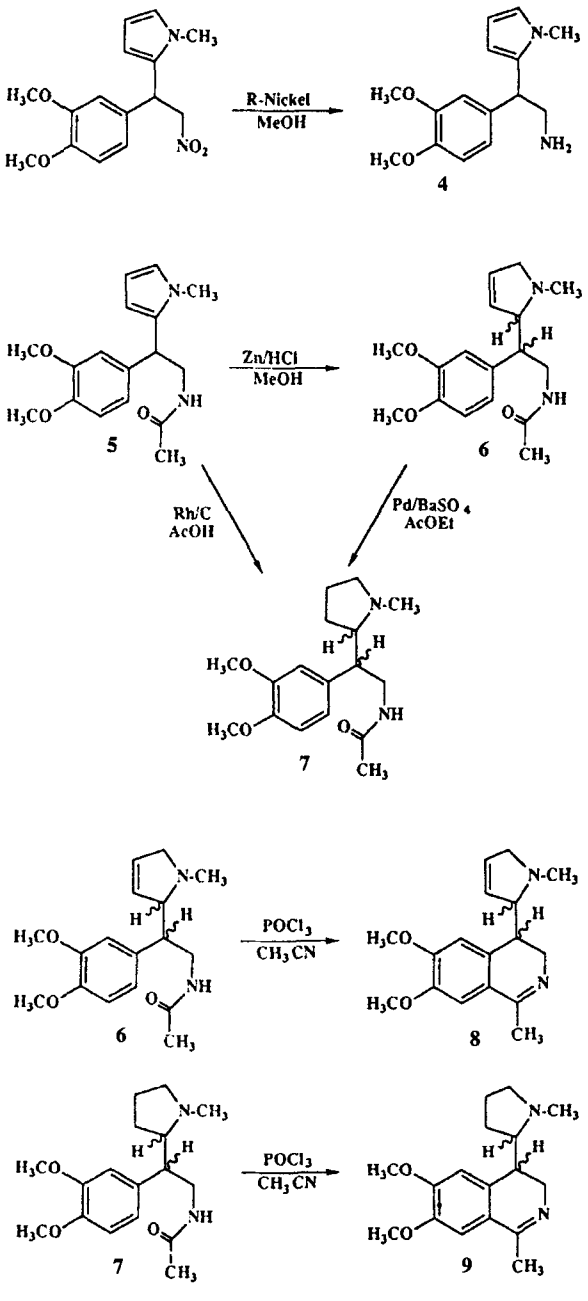
Pyrrolidine **9** was dehydrogenated according to lit.[1]. The mixture of compounds was separated by column chromatography: Et_2O/MeOH (9:1) led to two compounds, then a more polar fraction was separated by Et_2O/MeOH/NH_3 (20:4:1).

The compound with the lowest rf-value from the Et_2O/MeOH separation proved to be 6,7-dimethoxy-1-methylisoquinoline (**10**). The compound with the higher rf-value was identified as the rearranged molecule **11**. The formation of this benzo[*f*]indole might be rationalized as depicted in Scheme 4.



Scheme 1 **2** **1** **3**

  0365-6233/92/1010-0679 $ 3.50 + .25/0



Scheme 2

Dehydrogenation of cpd. **9** leads to an enamine. Allylic/azaallylic hydrogenolysis opens the isoquinoline ring, affording an imine increment, to which the enamine adds nucleophilically with its β-position. The iminium group is stabilized by deprotonation and aromatization - this might be the driving force - affording compound **11**.

Among the compounds eluted by the more polar solvent 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**12**) has the highest rf-value, followed by the pyrrolidinyl-isoquinoline **13**. The molecule with the lowest rf-value is starting material **9**.

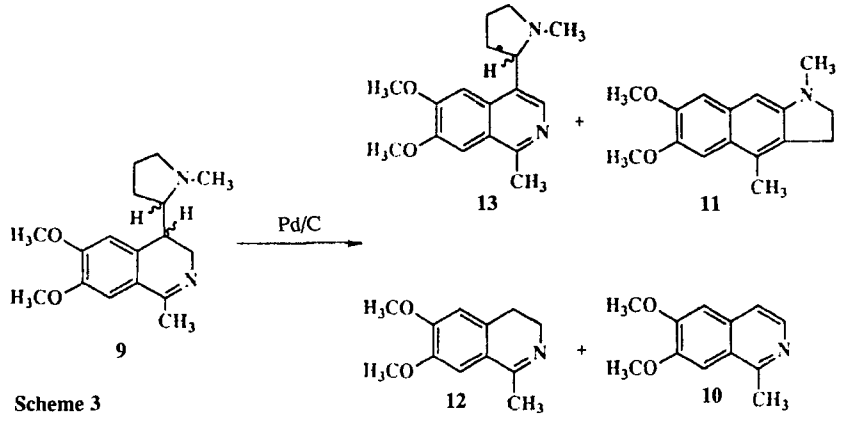
As can be seen from Scheme 3, our model compound **9** loses the pyrrolidine increment (cf. **10** and **12**). The 3,4-dihydroisoquinoline **12** seems to be an intermediate on the route to **10**, because **12** was dehydrogenated to the isoquinoline **10** in a separate experiment under identical conditions.

When we dehydrogenated the pyrroline derivative **8** under our standard conditions, it was aromatized in both ring systems leading to the 4-pyrrolylisoquinoline **14** (Scheme 5).

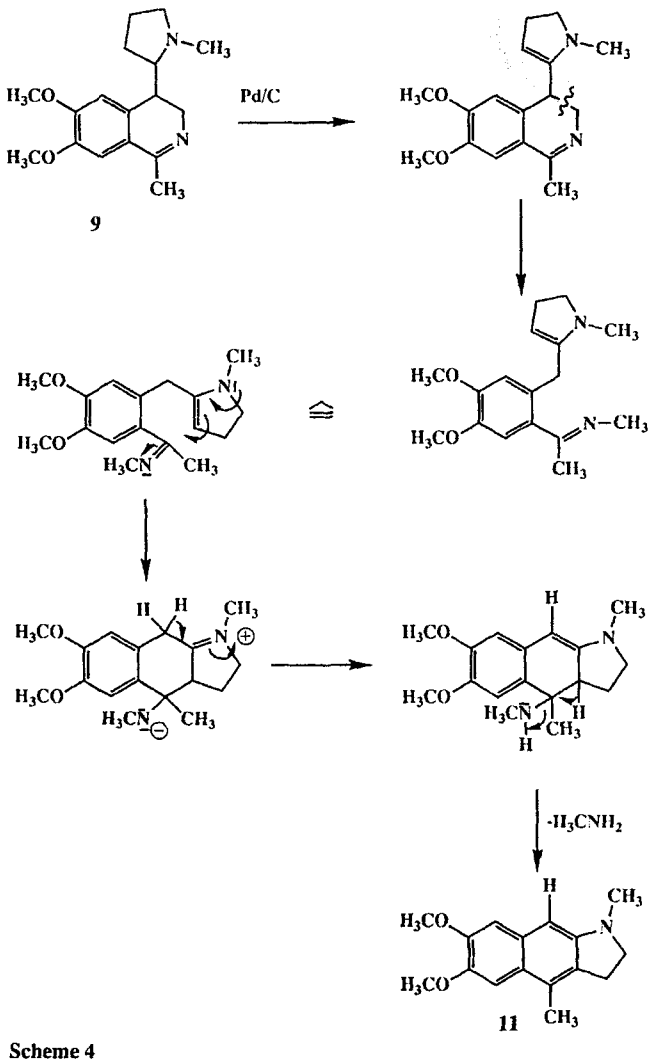
This dehydrogenation proceeds remarkably fast: the starting material **8** was consumed already after 20 min. It might be speculated that a shift of the double bond in **8** to the 2,3-position of the pyrroline group facilitates the aromatization of the isoquinoline system by a conjugative effect.

Volatile components

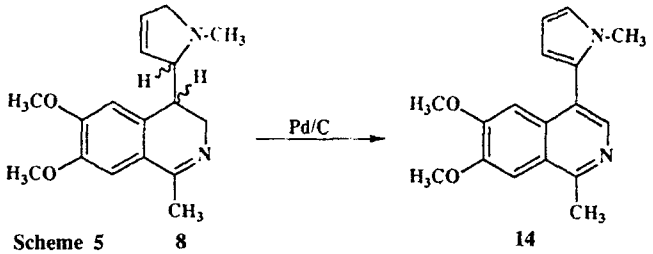
In a separate dehydrogenation experiment of **9** we trapped the volatile compounds in $CDCl_3$ of -30 °C in a NMR-tube cooled by dry ice. A mild stream of dried N_2 was used for transportation. By comparison with the spectra of Δ^3-*N*-methylpyrroline, *N*-methylpyrrolidine, *N*-methylpyrrol, and tetraline we found mainly *N*-methylpyrrolidine besides traces of tetraline. This deviates from the results obtained by GC-MS experiments with the macrostromine precursor **2**[5]. GC-measurements indicate that *N*-methylpyrrolidine is converted in small quantities only to *N*-methylpyrrol, Δ^3-*N*-methylpyrroline disproportionates, and *N*-methylpyrrol is partially di- and tetra-hydrogenated. These results point towards a removal of the pyrrolidine increment as *N*-methylpyrrolidine.



Scheme 3



Scheme 4



Scheme 5

Winterfeldt et al.[4] cleaved the pyrrolidine increment in their dihydroharman derivative by pivalic acid/trifluoroacetic acid. In *Winterfeldt's* case this H+-catalyzed cleavage of the pyrrolidine ring leads to the alkaloid brevicarine. For explanation see *Winterfeldt*[4]. - Our compound **9** reacts analogously affording the isoquinoline **15**. This indicates that this reaction may lead to alkaloids biogenetically related to macrostomine (**1**).

Moreover, these experiments show that the cleavage observed during Pd-catalyzed dehydrogenation of the macrostomine-precursor **2** seems to be characteristic for 3-(pyrrolidin-2-yl)-2,3-dihydropyridins.

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Experimental Part

General remarks: lit.[1b].- ^{1}H-NMR spectra in $CDCl_3$, δ in ppm.

N-[2-(N-Methylpyrrol-2-yl)-2-(3,4-dimethoxyphenyl)ethyl]-acetamide (5)

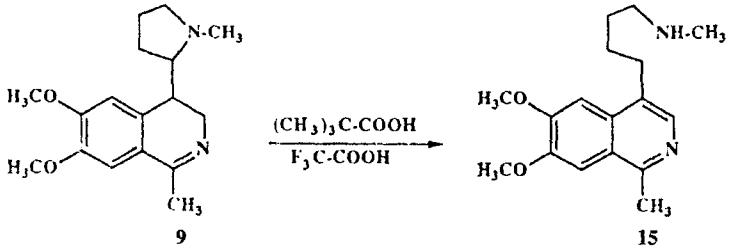
To the mixture of 3.8 g (14.6 mmole) of 2-(3,4-dimethoxyphenyl)-2-(*N*-methylpyrrol-2-yl)-ethylamine (**4**)[2] and 1.5 g (14.9 mmole) Et_3N in 25 ml absol. CH_2Cl_2, 1.5 g (14.6 mmole) acetic anhydride were added slowly drop by drop. Then the mixture was stirred for 1 h at room temp. Excess of Et_3N and its salt were removed by 2N HCl (2 x 10 ml). The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in Et_2O and crystallized in the refrigerator: 4.19 g (95%), colourless crystals, m.p. 136 °C (EtOH).- $C_{17}H_{22}N_2O_3$ (302.4) Calcd. C 67.5 H 7.33 N 9.3 Found C 67.2 H 7.30 N 9.3.- IR (KBr): 3300 (NH), 2840 (NCH_3), 1720 (CO) cm^{-1}.- ^{1}H-NMR: δ = 1.90 (s; 3H, $COCH_3$), 3.30 (s; 3H, NCH_3), 3.55-3.75 (m; 2H, CH_2), 3.80 and 3.85 (2 x s; 6H, OCH_3), 4.00-4.20 (m; 1H, CH), 5.80 (br. s; 1H, NH, D_2O-exchange), 6.10-6.90 (m; 6H, arom.).

Diastereomeric N-[2-(N-Methyl-Δ^3-pyrrolin-2-yl)-2-(3,4-dimethoxyphenyl)ethyl]-acetamides (6a and 6b)

To 1.49 (4.9 mmole) acetamide **5**, dissolved in 40 ml of MeOH, were added 2 g Zn dust. Then a solution of 14.5 ml 36% HCl in 50 ml MeOH was added in drops. The mixture was stirred for 30 min and 2 x 2 g Zn dust were added during this time. The mixture was diluted with 250 ml of water, extracted with 20 ml of CH_2Cl_2 (neutral compounds, discarded), basified with conc. NH_3 and extracted again with CH_2Cl_2. After drying (Na_2SO_4) and evaporation *in vacuo* the diastereomers were separated by cc (SiO_2; MeOH/Et_2O 1:1).

Diastereomer 6a

0.88 g (59%), m.p. 98-99 °C (Et_2O).- $C_{17}H_{24}N_2O_3$ (304.4) Calcd. C 67.1 H 7.90 N 9.2 Found C 67.1 H 7.90 N 9.2.- IR (KBr): 3300 (NH), 2800



Scheme 6

(NCH_3), 1725 (CO) cm^{-1}.- ^{1}H-NMR: δ = 1.90 (s; 3H, $COCH_3$), 2.50 (s; 3H, NCH_3), 2.80-3.90 (m; 6H, 2 x CH_2, 2 x CH), 3.95 (s; 6H, OCH_3), 5.55-5.90 (m; 2H, vinyl.), 6.65-6.80 (m; 3H arom.), 7.45 (br. s; 1H, NH, D_2O-exch.).

Diastereomer 6b

0.44 g (29%), m.p. 137 °C (Et_2O).- Found C 67.3 H 7.75 N 9.4.- IR (KBr): 3300 (NH), 2800 (NCH_3), 1725 (CO) cm^{-1}.- ^{1}H-NMR: δ = 1.90 (s; 3H, $COCH_3$), 2.40 (s; 3H, NCH_3), 2.65-3.80 (m; 6H, 2 x CH_2, 2 x CH), 3.85 (s; 6H, OCH_3), 5.40-5.85 (m; 2H, vinyl.), 6.65-6.95 (m; 3H arom.), 7.15 (br. s; 1H, NH, D_2O-exch.).

N-[2-(N-Methylpyrrolidin-2-yl)-2-(3,4-dimethoxyphenyl)ethyl]-acetamides (7)

Mixture of diastereomers 1:1 (^{1}H-NMR).

Method A

0.5 g (1.7 mmole) of the 1:1 mixture of diastereomeric pyrroline derivatives **6** were hydrogenated in 50 ml of AcOEt over 74 mg $Pd/BaSO_4$ (5%) at room temp. and 1 atm. under stirring until H_2-uptake ceased. After filtration and evaporation 0.46 g (91%) of **7**.

Method B

The solution of 0.83 g (2.75 mmole) acetamide **5** in 10 ml of glacial acetic acid was mixed with 150 mg Rh/C (5%) and stirred in an autoclave at 10 bar H_2 for 12 h. After filtration the filtrate was diluted with 80 ml of water, basified with 3N NaOH and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*: 0.79 g **7** (94%), colourless crystals, m.p. range 108-114 °C (Et_2O).- $C_{17}H_{26}N_2O_3$ (306.4) Calcd. C 66.6 H 8.55 N 9.1 Found C 66.5 H 8.46 N 9.1.- IR (KBr): 3300 (NH), 2800 (NCH_3), 1725 (CO) cm^{-1}.- ^{1}H-NMR: δ = 1.40-1.80 (m; 4H, N-CH-$C\underline{H}_2$-$C\underline{H}_2$), 1.90 (s; 3H, $COCH_3$), 2.35 and 2.40 (2 x s; 3H, NCH_3), 2.40-3.75 (m; 5H, 2 x CH_2, CH), 3.80 and 3.85 (2 x s; 6H, OCH_3), 6.55-6.85 (m; 3H arom.), 7.60 (br. s; 1H, NH, D_2O-exch.).

1-Methyl-4-(N-methylpyrrolidin-2-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline (9)

6 g (19.6 mmole) acetamide **7** (1:1 mixture of diastereomers) in 25 ml of absol. CH_3CN were refluxed with 6.5 ml of $POCl_3$ for 3 h. Then excess of $POCl_3$ and solvent were removed *in vacuo*. The residue was dissolved in 100 ml of ice water, the solution was basified with 3N NaOH and extracted with $CHCl_3$. After drying (Na_2SO_4) and evaporation the residue was purified by cc (SiO_2; $CHCl_3$/EtOH/NH_3 85:14:1) and subsequent kugelrohr distillation: 3.27 g (58%), mixture of diastereomers (1:1), colourless oil, b.p. 150 °C ($1 \cdot 10^{-3}$ torr).- $C_{17}H_{24}N_2O_2$ (288.4) Calcd. C 70.8 H 8.39 N 9.7 Found C 70.7 H 8.46 N 9.6.- IR (film): 2800 (NCH_3), 1640 (C=N) cm^{-1}.- ^{1}H-NMR: δ = 1.45-1.75 (m; 4H, N-CH-$C\underline{H}_2$-$C\underline{H}_2$), 2.10 (s; 3H, C-CH_3), 2.15-4.15 (m; 5H, 2 x CH_2, CH), 2.35 and 2.40 (2 x s; 3H, NCH_3), 3.90 and 3.95 (2 x s; 6H, OCH_3), 6.75 (s; 0.5 H arom.), 6.95 (s; 1H arom.), 7.10 (s; 0.5 H arom.).

1-Methyl-4-(N-methyl-Δ^3-pyrrolin-2-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline (8)

2.5 g (8.2 mmole) **6** (mixture of diastereomers 1:1) were reacted as described for the preparation of **9**.- Purification by cc (SiO_2; Et_2O/MeOH/NH_3 20:4:1) and kugelrohr distillation: 1 g (42%) **8**, mixture of diastereomers 1:1; colourless oil, b.p. 140 °C ($1 \cdot 10^{-3}$ torr).- $C_{17}H_{22}N_2O_2$ (286.4) Calcd. C 71.3 H 7.74 N 9.8 Found C 71.2 H 7.47 N 9.4.- IR (film): 2800 (NCH_3), 1640 (C=N) cm^{-1}.- ^{1}H-NMR: δ = 2.35 and 2.40 (s; 3H, C-CH_3), 2.50 (s; 3H, NCH_3), 3.10-4.40 (m; 6H, 2 x CH_2, 2 x CH), 3.95 (s; 6H, OCH_3), 5.35-5.85 (m; 2H vinyl.), 6.80 (s; 1H arom.), 7.05 (s; 1H arom.).

Dehydrogenations, general procedure

0.4 mmole of the pertinent 3,4-dihydroisoquinoline were dissolved in 5 ml of tetraline and dehydrogenated under N_2 with 100 mg Pd/C (10%) for 2 h at 190 °C.- After cooling to room temp. the catalyst was removed by filtration and washed with Et_2O. Basic compounds were extracted from this mixture by 10 ml 2N HCl, the org. phase was discarded. The water phase was alkalized by sat. $NaHCO_3$-solution and extracted with CH_2Cl_2. This solution was dried (Na_2SO_4) and evaporated *in vacuo*. Products were separated by cc.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (12)

Cleavage product from **9**; cc separation (SiO_2; Et_2O/MeOH/NH_3 20:4:1), 14%, colourless crystals, m.p. 105 °C (petroleum ether); lit.[6]: 108 °C.- $C_{12}H_{15}NO_2$ (205.3) Calcd. C 70.2 H 7.37 N 6.8 Found C 70.0 H 7.39 N 6.7.- IR (film): 1640 (C=N) cm^{-1}.- ^{1}H-NMR: δ = 2.35 (s; 3H, C-CH_3), 2.65 (t; J = 7.5 Hz, 2H, N-CH_2-$C\underline{H}_2$), 3.65 (t; J = 7.5 Hz, 2H, N-CH_2), 3.95 (s; 6H, OCH_3), 6.75 (s; 1H arom.), 7.05 (s; 1H arom.).

6,7-Dimethoxy-1-methylisoquinoline (10)

Cleavage product from **9**; cc separation (SiO_2; Et_2O/MeOH 9:1), 14%.- From dehydrogenation of **12**: 96%.- Colourless crystals, m.p. 105-106 °C (petroleum ether); lit.[7]: 107-108 °C.- $C_{12}H_{13}NO_2$ (203.2) Calcd. C 70.9 H 6.45 N 6.9 Found C 70.5 H 6.50 N 6.8.- ^{1}H-NMR: δ = 2.85 (s; 3H, C-CH_3), 4.00 (s; 6H, OCH_3), 7.00 (s; 1H arom.), 7.25 (s; 1H arom.), 7.35 (AB; J_{AB} = 6 Hz, 1H, H-4), 8.25 (AB; J_{AB} = 6 Hz, 1H, H-3).

6,7-Dimethoxy-1-methyl-4-(N-methylpyrrolidin-2-yl)isoquinoline (13)

Cleavage product from **9**; cc separation (SiO_2; Et_2O/MeOH/NH_3 20:4:1), 19%, colourless oil, b.p. 145 °C, $1 \cdot 10^{-3}$ torr.- $C_{17}H_{22}N_2O_2$ (286.4) Calcd. C 71.3 H 7.74 N 9.8 Found C 71.2 H 7.49 N 9.6.- IR (film): 2800 (NCH_3), 1640 (C=N) cm^{-1}.- ^{1}H-NMR: δ = 1.60-3.30 (m; 7H, pyrr.), 2.40 (s; 3H, NCH_3), 2.85 (s; 3H, C-CH_3), 4.00 (s; 6H, OCH_3), 7.20 (s; 1H arom.), 7.30 (s; 1H arom.), 8.20 (s; 1H, H-3).

2,3-Dihydro-6,7-dimethoxy-1,4-dimethylbenzo[f]indol (11)

Cleavage product from **9**; cc separation (SiO_2; Et_2O/MeOH 9:1), 5%; colourless crystals, m.p. 156 °C (Et_2O).- $C_{16}H_{19}NO_2$ (257.3).- HR-MS: Calcd. 257.14156 Found 257.14104.- IR (film): 2810 (NCH_3), 1630 (C=C) cm^{-1}.- ^{1}H-NMR: δ = 2.50 (s; 3H, NCH_3), 2.85 (s; 3H, C-CH_3), 2.90-3.15 (m; 2H, CH_2), 3.25-3.50 (m; 2H, CH_2), 4.00 (s; 6H, OCH_3), 6.50 (s; 1H arom., H-9), 7.00 (s; 1H arom.), 7.20 (s; 1H arom.).

6,7-Dimethoxy-1-methyl-4-(N-methylpyrrol-2-yl)isoquinoline (14)

By dehydrogenation of **8**, purification by cc (SiO_2; Et_2O/MeOH/NH_3 20:4:1), 30%, colourless oil, b.p. 130 °C, $1 \cdot 10^{-3}$ torr.- $C_{17}H_{18}N_2O_2$ (282.3).- IR (film): 2810 (NCH_3), 1620 (C=N) cm^{-1}.- ^{1}H-NMR: δ = 2.90 (s; 3H, C-CH_3), 3.45 (s; 3H, NCH_3), 3.90 and 4.05 (2 x s; 6H, OCH_3), 6.30-6.45 (m; 2H, H-3', H-4'), 6.80-6.95 (m; 1H, H-5'), 7.05 (s; 1H arom.), 7.35 (s; 1H arom.), 8.25 (s; 1H, H-3).

Volatile components from dehydrogenation of 9

The dehydrogenation was performed as described for the preparation of the non-volatile components. Volatile materials were removed from the reaction vessel by a slow stream of N_2 and trapped at -30 °C in 1 ml of

$CDCl_3$ (^{1}H-NMR analysis) or 1 ml of CH_3CN (gc).- GC-conditions: apparatus: Packard-Becker, B.V. (Delft), 428, reconstructed for capillary column; FID. Column temp. 250 °C, injector temp. 220 °C, detector temp. 250 °C. Injections volume 0.01 ml. Split 1:100. Column pressure 0.2 MP, H_2.- Retention times: *N*-methylpyrrolidine 6.63 min, *N*-methylpyrroline 7.34 min, *N*-methylpyrrol 14.9 min.

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[Ph 998]