Constituents of Tropical Medicinal Plants, LXIII[1)+]:

Synthesis of 2-Methoxyonychine Alkaloids - Structure Revision of Oxylopidine

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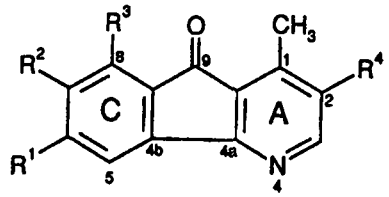
Received May 9, 1994

Condensation of β-aminocinnamic acid esters with 3-chloro-2-methoxycrotonaldehyde opened an easy access to 2-phenyl-5-methoxy-4-methylnicotinic acid esters which were cyclized by polyphosphoric acid to yield the corresponding 2-methoxyonychines. By this method a number of 2-methoxy-substituted onychines were prepared for the first time, i.a. oxylopidine, the structure of which has to be revised.

Inhaltsstoffe tropischer Arzneipflanzen, 63. Mitt.[1)]:
Synthese von 2-Methoxyonychin-Alkaloiden - Strukturrevision des Oxylopidins

Onychin-Alkaloide (= 1-Methyl-4-azafluoren-9-one) zeichnen sich teilweise durch antifungische Eigenschaften aus. Kondensation von β-Aminozimtsäureestern mit 3-Chlor-2-methoxycrotonaldehyd in Gegenwart von Triethylamin führte zu 5-Methoxy-4-methyl-2-phenylnicotinsäureestern, deren Cyclisierung mit Polyphosphorsäure erstmals auch 2-Methoxyonychine und u.a. auch Oxylopidin zugänglich machte. Die gemessenen Daten verlangen eine Strukturrevision für Oxylopidin.

The onychines constitute a group of alkaloids which only recently have been detected and which - up-to-now - have only been isolated from plants of the *Annonaceae* family[2,3)]. Structurally, the onychines represent 1-methyl-4-aza-fluoren-9-ones*) (Fig. 1), and their structures vary in degree and position of hydroxylation and/or methoxylation which occurs mainly at ring C[3)].



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	R^1	R^2	R^3	R^4
1a	H	H	H	OCH_3
1b	H	OCH_3	H	OCH_3
1c	H	OH	H	OCH_3
1d	OCH_3	OH	H	OCH_3
1e	OH	OCH_3	H	OCH_3
1f	H	OH	OCH_3	OCH_3
1g	H	OH	H	OH

Fig. 1: Onychine (**1**: all R = H) and structures of the synthesized 2-methoxy-(or 2-hydroxy)onychine alkaloids.

In a preceeding paper we have described the isolation of the new onychines **1c**, **1f**, and **1g** from *Piptostigma fugax* (*Annonaceae*), whose common structural feature consists in an oxygen substituent at C-2[1)].

Since these alkaloids occur in low concentrations only and in respect to their potential biological activity[5)] we have dealt with their synthesis[6)].

2-Methoxy substituted onychines are not accessible by known synthetic routes. Therefore, we modified *Taylor's* method[7)], which reacts β-aminocinnamic acid esters **2** with crotonaldehyde to prepare 4-methyl-2-phenylnicotinic acid esters as key intermediates for a subsequent intramolecular cyclisation. Use of 3-chlorocrotonaldehyde[8)] instead of crotonaldehyde not only improves the yield of 5-unsubstituted **4** (for the synthesis of onychine) from 10 to > 50% but also opens an access to the corresponding 5-methoxy-4-methylnicotinic acid esters **4** in up to 90% yield, when 3-chloro-2-methoxycrotonaldehyde (**3**)[9)] is employed (Fig. 2).

The reaction of **2** with **3** to prepare solely **4** and not its regioisomer **5** can obviously be directed by the auxilliary base used: in the presence of triethylamine, **4** was always the only product, but **2a** with **3** in the presence of pyridine gave only **5**.

The final intramolecular cyclisation of **4** to the 2-methoxyonychines was brought about by polyphosphoric acid (PPA). Thus, **1a** was prepared from **2a** and **3** *via* **4a** in an overall yield > 80% and in 90% yield for the PPA cyclisation step. However, a substituted phenyl ring in **4** decreased the yield of the PPA-induced cyclisation significantly: **4b** (R^1 = H, R^2 = OCH_3) afforded **1b** in only 60% yield, while **4c** (R^1 = H, R^2 = OH) further decreased the yield to 30%

+) Dedicated to Prof. Dr. *H.J. Roth*, Tübingen, Germany, on the occasion of his 65th birthday.

*) Polylongine, a corresponding 1-methyl-4-aza-fluoren-9-ol has also been isolated from a plant[4)].

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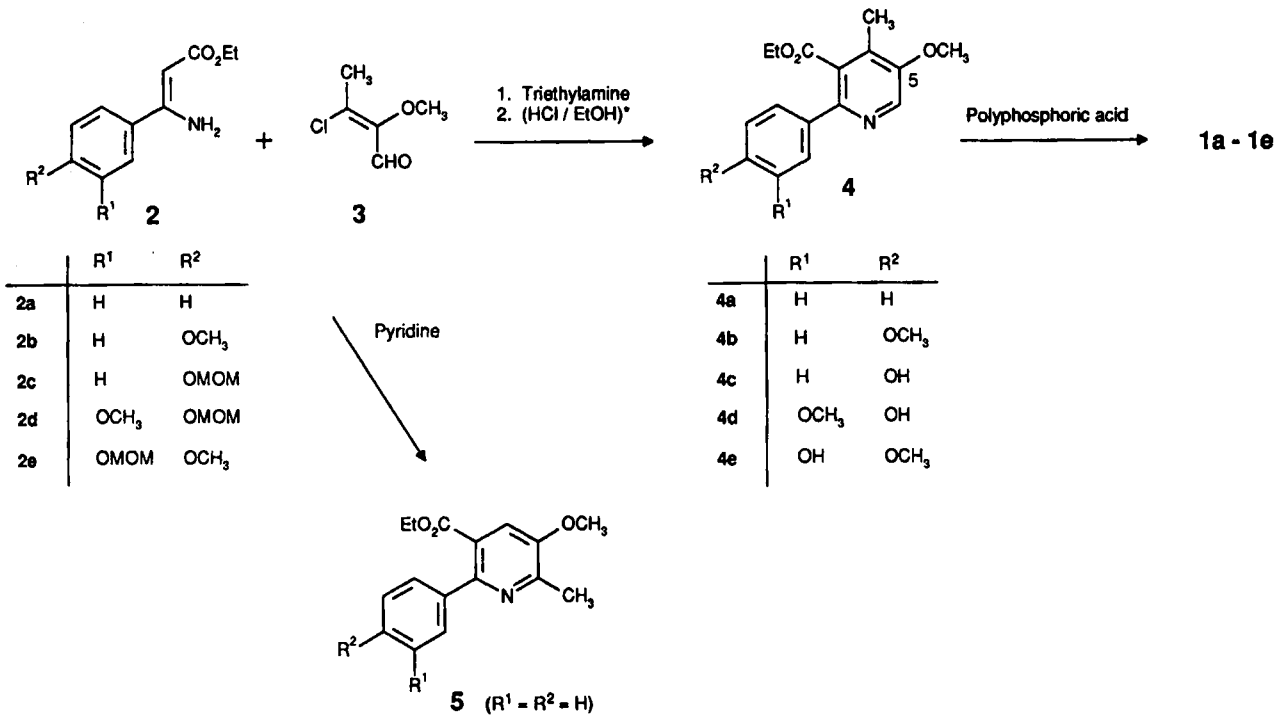

	R¹	R²
2a	H	H
2b	H	OCH_3
2c	H	OMOM
2d	OCH_3	OMOM
2e	OMOM	OCH_3

	R¹	R²
4a	H	H
4b	H	OCH_3
4c	H	OH
4d	OCH_3	OH
4e	OH	OCH_3

Fig. 2: Cycloreaction of β-aminocinnamic acid esters **2** with 3-chloro-2-methoxycrotonaldehyde (**3**) to the corresponding 5-methoxy-4-methyl-2-phenylnicotinic acid esters **4** and further conversion to the onychines **1a** to **1e** (* Reaction step only when MOM-protected OH-groups were involved.)

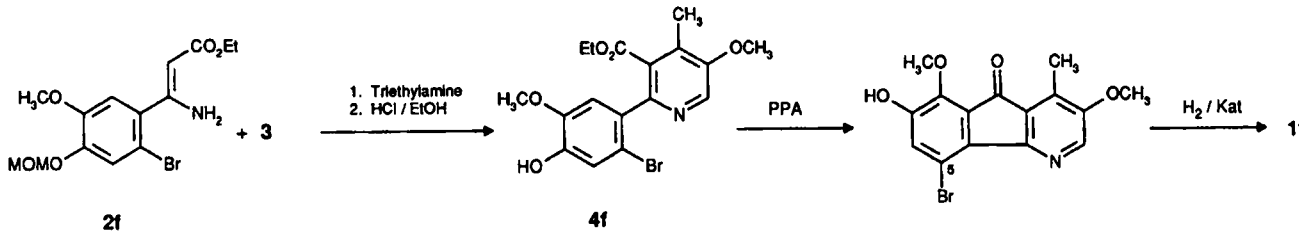

Fig. 3: Preparation of the 8-substituted 2-methoxyonychine **1f** from **2f** *via* the 2-(2'-bromophenyl)-5-methoxy-4-methylnicotinic acid ester **4f**.

and the OH-group, when derivatized by MOM inhibited the cyclisation reaction almost completely.

Cleavage of the methoxy groups in **1b** with HBr/AcOH produced **1g**, one of the natural onychines recently isolated from *Piptostigma fugax*[1].

However, when **4d** (or **4e**) with an asymmetrical substitution at the phenyl ring was subjected to intramolecular cyclisation, the expected[10] mixture of the isomers **1d** and **1f** was not achieved: the reaction occurred exclusively at the less hindered C-atom and yielded from **4d** the 6,7-substituted 2-methoxy-onychine **1d** only.

1d represents the structure recently claimed[10] for oxylopidine[11] from *Oxandra xylopioides* (*Annonaceae*). Since the physicochemical data reported for this onychine alkaloid show discrepancies to the properties observed for **1d**, we also synthesized **1e** (from **4e**) and found the data of this compound consistent with those published for oxylopidine. Consequently, the structure of oxylopidine needs to be revised.

To prepare 8-substituted 2-methoxyonychines like **1f**, the *ortho*-position in the phenyl ring of **4**, which should be prevented from reaction, was blocked by bromine[12]. With the 2-(2'-bromophenyl)nicotinic acid ester **4f** we achieved 5-bromo-7-hydroxy-2,8-dimethoxyonychine (5-bromo-**1f**), from which the bromine was removed by catalytic hydrogenation (Fig. 3).

The β-aminocinnamic acid ethyl esters **2** used for the synthesis of **4** were prepared from the corresponding benzonitriles by a modified *Blaise*-reaction[13] with bromoacetic acid ethyl ester and zinc. Phenolic hydroxy groups in the benzonitriles were protected as MOM-ethers and the corresponding MOM-protected β-aminocinnamic acid ethyl esters **2** were subjected to the reaction with **3** in the presence of triethylamine. Removal of the protecting groups was brought about by treatment with HCl/EtOH.

Experimental Part

General Remarks

Mps: uncorrected.- Analytical TLC: precoated plates (Nano plates Sil-20 UV, Macherey-Nagel); detection: UV-254 nm, R-1 = 2,4-dinitrophenylhydrazine[14], R-2 = *p*-dimethylaminobenzaldehyde[15], R-3 = *Dragendorff's* reagent[16].- Unless otherwise stated, UV/VIS-spectra were measured in MeOH; IR in $CHCl_3$.- EIMS and HREIMS: 70 eV; if not otherwise stated, fragments with m/z > 40 and rel. int. > 10% were specified. Rel. intensities in %.- If not indicated otherwise, ^{1}H-NMR were measured at 360 MHz and ^{13}C-NMR at 90 MHz in $CDCl_3$, TMS as int. standard.

3-Chloro-2-methoxycrotonaldehyde (**3**, *mixture of stereoisomers*)

From 9.2 ml (8.8 g, 0.1 mol) methoxyacetone in DMF/$POCl_3$ according to Lit.[8,9]. After addition of ice the mixture was extracted with CH_2Cl_2. The combined org. layers on evaporation *in vacuo* yielded 8.80 g **3** (67%), colourless oil which is stable when stored as a solution (10%) in CH_2Cl_2.- For analytical characterization 1 g of **3** was separated chromatographically (MPLC, silica gel, pentane-CH_2Cl_2 (3:2)) to give the *E*-isomer **3a** and the *Z*-isomer **3b** in ca. 1:1 ratio.

3a *(E-isomer)*

Yield 0.42 g, colourless oil.- TLC: Rf 0.37 (pentane-CH_2Cl_2 (1:1)), R-1: orange.- IR: $\tilde{\nu}$max = 1711, 1687 cm^{-1} (α,β-unsaturated CO).- UV: λmax (lg ε) = 260 nm (3.44).- ^{1}H-NMR: δ (ppm) = 2.34 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 10.06 (s, 1H, 1-H).- ^{13}C-NMR: δ (ppm) = 21.6 (C-4), 60.2 (OCH_3), 142.2 (C-3), 150.0 (C-2), 185.6 (C-1).- MS: m/z (rel.Int.) = 136 (31, $M_1^{+\cdot}$), 134 (96, $M_2^{+\cdot}$), 106 (12), 104 (38), 92 (10), 90 (30), 69 (100), 63 (30), 62 (27), 55 (48), 49 (18), 41 (23).

3b *(Z-isomer)*

Yield 0.44 g; colourless oil.- TLC: Rf 0.32 (pentane-CH_2Cl_2 (1:1)); R-1: positive.- IR: $\tilde{\nu}$max = 1711; 1686 cm^{-1} (α,β-unsaturated CO).- UV: λmax (lg ε) = 255 nm (3.59).- ^{1}H-NMR: δ (ppm) = 2.53 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 9.82 (s, 1H, 1-H).- Diff. NOE:

irradiation on:	NO-enhancement observed on:
1-H	OCH_3, CH_3
OCH_3	1-H
CH_3	1-H

^{13}C-NMR: δ (ppm) = 20.8 (C-4), 59.9 (OCH_3), 142.5 (C-3), 150.2 (C-2), 183.7 (C-1).- MS: m/z (rel.Int.) = 136 (23, $M_1^{+\cdot}$), 134 (70, $M_2^{+\cdot}$), 106 (15), 105 (9), 104 (47), 90 (28), 69 (100), 68 (7), 63 (31), 62 (28), 61 (15), 55 (54), 53 (11), 49 (13), 43 (11), 41 (23), 39 (48).

β-Aminocinnamic acid ethyl ester (**2a**)

From 5.15 g (0.05 mol) benzonitrile and an excess of ethoxycarbonylmethyl zinc bromide in THF[13]. After work up with K_2CO_3-solution the combined tetrahydrofuran layers were subjected to centrifugation to precipitate $ZnCO_3$. Purification by MPLC on silica gel (hexane-acetone (9:1)).- Yield 7.42 g (78%); colourless oil.- TLC: Rf 0.35 (hexane-acetone (4:1)); R-2: pink (without heating).- IR: $\tilde{\nu}$max = 3500, 3335 (NH), 1661 cm^{-1} (CO).- UV: λmax (lg ε) = 201 (4.01), 231 (3.90), 301 nm (3.99).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.20 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 4.06 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 4.78 (s, 1H, α-H), 7.25 (br s, 1H, N-H), 7.51-7.59 (m, 3H, 3-H, 4-H, 5-H), 7.64 (m, 2H, 2-H, 6-H), 8.06 (br s, 1H, N-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 57.9 ($O\underline{C}H_2CH_3$), 81.4 (C-α), 126.4 (C-3, C-5), 128.6 (C-2, C-6), 130.2 (C-4), 135.8 (C-1), 160.8 (C-β), 169.4 (-CO_2-).- MS: m/z (rel.Int. > 20%) = 191 (80, $M^{+\cdot}$), 146 (59), 119 (100), 104 (61), 103 (31), 91 (34), 77 (27), 51 (22), 43 (20).

β-Amino-4-methoxycinnamic acid ethyl ester (**2b**)

From 6.65 g (0.05 mol) 4-methoxybenzonitrile as described for **2a**. Purification by MPLC on silica gel (hexane-acetone (9:1)).- Yield 7.95 g (72%); colourless oil.- TLC: Rf 0.40 (hexane-acetone (4:1)); R-2: pink.- IR: $\tilde{\nu}$max = 3502, 3337 (NH), 1657 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 204 (3.98), 248 (3.75), 304 nm (4.01).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.19 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.80 (s, 3H, OCH_3), 4.04 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 4.76 (s, 1H, α-H), 6.99 (**AA'BB'**, 2H, 3-H, 5-H), 7.2 (br s, 1H, N-H), 7.57 (**AA'BB'**, 2H, 2-H, 6-H), 8.0 (br s, 1H, N-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 55.3 (OCH_3), 57.8 ($O\underline{C}H_2CH_3$), 80.3 (C-α), 113.9 (C-3, C-5), 127.8 (C-2, C-6), 128.4 (C-1), 160.4 (C-4), 160.9 (C-β), 169.5 (-CO_2-).- MS: m/z (rel.Int.) = 221.1052 (calcd. for $C_{12}H_{15}NO_3$: 221.1052) (32, $M^{+\cdot}$), 176 (55), 150 (11), 149 (100), 135 (20), 134 (73), 133 (31).

β-Amino-4-(methoxymethyloxy)cinnamic acid ethyl ester (**2c**)

1. *4-(Methoxymethyloxy)benzonitrile*

From 11.9 g (0.1 mol) 4-hydroxybenzonitrile according to lit.[17].- Yield 11.6 g (71%); pale yellow oil.- TLC: Rf 0.31 (hexane-acetone (3:2)).- IR: $\tilde{\nu}$max = 2229 cm^{-1} (CN).- UV: λmax (lg ε) = 202 (3.90), 225 (3.92), 278 nm (2.88).- ^{1}H-NMR: δ (ppm) = 3.48 (s, 3H, $OCH_2O\underline{CH_3}$), 5.22 (s, 2H, $OC\underline{H_2}OCH_3$), 7.10 (**AA'BB'**, 2H, 3-H, 5-H), 7.59 (**AA'BB'**, 2H, 2-H, 6-H).- ^{13}C-NMR: δ (ppm) = 56.3 ($OCH_2O\underline{C}H_3$), 94.2 ($O\underline{C}H_2OCH_3$), 105.1 (C-1), 116.7 (C-3, C-5), 118.9 (CN), 133.9 (C-2, C-6), 160.5 (C-4).- MS: m/z (rel.Int.) = 163.0633 (calcd. for $C_9H_9NO_2$: 163.0633) (27, $M^{+\cdot}$), 102 (11), 85 (14), 83 (21), 45 (100).

2. *β-Amino-4-(methoxymethyloxy)cinnamic acid ethyl ester* (**2c**)

From 3.26 g (0.02 mol) 4-(methoxymethyloxy)benzonitrile as described for **2a**. Purification by MPLC on silica gel (hexane-acetone (4:1)).- Yield 3.22 g (64%); pale yellow oil.- TLC: Rf 0.42 (hexane-acetone (3:2)); R-2: pink.- IR: $\tilde{\nu}$max = 3501, 3334 (NH), 1658 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 2.04 (4.10), 246 (3.90), 303 (4.16); + HCl: 204 (3.95), 238 (3.77), 244 (sh, 3.77), 306 nm (4.14).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.19 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.38 (s, 3H, $OCH_2O\underline{CH_3}$), 4.05 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 5.24 (s, 2H, $OC\underline{H_2}OCH_3$), 4.75 (s, 1H, α-H), 7.06 (**AA'BB'**, 2H, 3-H, 5-H), 7.2 (br s, 1H, N-H), 7.57 (**AA'BB'**, 2H, 2-H, 6-H), 8.0 (br s, 1H, N-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 55.6 ($OCH_2O\underline{C}H_3$), 57.8 ($O\underline{C}H_2CH_3$), 80.6 (C-α), 93.6 ($O\underline{C}H_2OCH_3$), 115.9 (C-3, C-5), 127.8 (C-2, C-6), 129.7 (C-1), 158.3 (C-4), 160.4 (C-β), 169.5 (-CO_2-).- MS: m/z (rel.Int.) = 251.1158 (calcd. for $C_{13}H_{17}NO_4$: 251.1157) (82, $M^{+\cdot}$), 206 (16), 179 (73), 178 (23), 162 (119), 161 (22), 149 (11), 133 (12), 45 (100).

β-Amino-3-methoxy-4-(methoxymethyloxy)cinnamic acid ethyl ester (**2d**)

1. *3-Methoxy-4-(methoxymethyloxy)benzonitrile*

From 14.9 g (0.1 mol) vanillonitrile according to lit.[17]. Purification by MPLC on silica gel (hexane-acetone (3:2)).- Yield 7.33 g (38%); white crystals.- Mp. 68-70°C (hexane-acetone).- TLC: Rf 0.27 (hexane-acetone (3:2)).- $C_{10}H_{11}NO_3$ (193.2) Calcd. C 62.2 H 5.74 N 7.3 Found C 62.0 H 5.74 N 7.1.- IR: $\tilde{\nu}$max = 2225 cm^{-1} (CN).- UV: λmax (lg ε) = 213 (4.32), 250 (3.95), 286 (3.49), 293 nm (3.49).- ^{1}H-NMR: δ (ppm) = 3.51 (s, 3H, $OCH_2O\underline{CH_3}$), 3.91 (s, 3H, 3-OCH_3), 5.29 (s, 2H, $OC\underline{H_2}OCH_3$), 7.12 (d, 1H, J = 2.5 Hz, 2-H), 7.20 (d, 1H, J = 9 Hz, 5-H), 7.25 (dd, 1H, J_1 = 9, J_2 = 2.5 Hz, 6-H).- ^{13}C-NMR: δ (ppm) = 56.2 and 56.5 ($OCH_2O\underline{C}H_3$ and 3-OCH_3), 95.1 ($O\underline{C}H_2OCH_3$), 105.3 (C-1), 114.6 (C-2), 115.7 (C-5), 119.0 (CN), 126.2 (C-6), 149.7 (C-4), 150.5 (C-3).- MS: m/z (rel.Int.) = 193 (22, $M^{+\cdot}$), 45 (100).

2. *β-Amino-3-methoxy-4-(methoxymethyloxy)cinnamic acid ethyl ester* (**2d**)

From 3.86 g (0.02 mol) 3-methoxy-4-(methoxymethyloxy)benzonitrile as described for **2a**. Purification by MPLC on silica gel (hexane-acetone

(4:1)).- Yield 3.43 g (61%); colourless oil.- TLC: Rf 0.35 (hexane-acetone (3:2)); R-2: pink.- IR: $\tilde{\nu}$max = 3500, 3334 (NH), 1658 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 215 (4.26), 254 (3.84), 305 (4.23); + HCl: 212 (4.11), 236 (3.94), 304 (4.10), 350 nm (3.79).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.18 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.38 (s, 3H, $OCH_2OC\underline{H}_3$), 3.83 (s, 3H, 3-OCH_3), 4.03 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.79 (s, 1H, α-H), 5.18 (s, 2H, $OC\underline{H}_2OCH_3$), 7.09 (d, 1H, J = 8 Hz, 5-H), 7.15 (dd, 1H, J_1 = 8, J_2 = 2 Hz, 1H, 6-H), 7.19 (d, 1H, J = 2 Hz, 2-H), 7.2 and 8.0 (each br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 55.6 and 55.7 (3-OCH_3 and $OCH_2O\underline{C}H_3$), 57.9 ($O\underline{C}H_2CH_3$), 80.7 (C-α), 94.6 ($O\underline{C}H_2OCH_3$), 110.5 (C-2), 116.0 (C-5), 118.9 (C-6), 130.4 (C-1), 147.5 (C-4), 149.4 (C-3), 160.5 (C-β), 169.5 (-CO_2-).- MS: m/z (rel.Int.) = 281.1263 (calcd. for $C_{14}H_{19}NO_5$: 281.1263) (57, $M^{+\cdot}$), 236 (17), 191 (28), 190 (35), 176 (13), 175 (17), 174 (22), 173 (25), 162 (15), 45 (100).

β-Amino-4-methoxy-3-(methoxymethyloxy)cinnamic acid ethyl ester (**2e**)

1. *4-Methoxy-3-(methoxymethyloxy)benzonitrile*

From 14.9 g (0.1 mol) isovanillonitrile according to lit.[17]. Purification by MPLC on silica gel ($CHCl_3$-hexane (1:1)).- Yield 16.6 g (86%); beige crystals.- Mp. 62-64°C (MeOH).- TLC: Rf 0.16 ($CHCl_3$-hexane (1:1)).- $C_{10}H_{11}NO_3$ (193.2) Calcd. C 62.2 H 5.74 N 7.3 Found C 62.4 H 5.87 N 7.3.- IR: $\tilde{\nu}$max = 2229 cm^{-1} (CN).- UV: λmax (lg ε) = 212 (4.15), 251 (3.39), 284 nm (3.13).- ^{1}H-NMR: δ (ppm) = 3.52 (s, 3H, $OCH_2OC\underline{H}_3$), 3.93 (s, 3H, 4-OCH_3), 5.24 (s, 2H, $OC\underline{H}_2OCH_3$), 6.93 (d, 1H, J = 8.5 Hz, 5-H), 7.33 (dd, 1H, J_1 = 8.5, J_2 = 2.5 Hz, 6-H), 7.42 (d, 1H, J = 2.5 Hz, 2-H).- ^{13}C-NMR: δ (ppm) = 56.1 and 56.4 (4-OCH_3 and $OCH_2O\underline{C}H_3$), 95.6 ($O\underline{C}H_2OCH_3$), 104.1 (C-1), 111.8 (C-5), 119.0 (CN), 119.3 (C-2), 127.7 (C-6), 146.7 (C-3), 153.5 (C-4).- MS: m/z (rel.Int.) = 193 (19, $M^{+\cdot}$), 45 (100).

2. *β-Amino-4-methoxy-3-(methoxymethyloxy)cinnamic acid ethyl ester* (**2e**)

From 3.86 g (0.02 mol) 4-methoxy-3-(methoxymethyloxy)benzonitrile as described for **2a**. Purification by MPLC on silica gel (hexane-acetone (4:1)).- Yield 3.20 g (57%); white needles.- Mp. 92-94°C (hexane).- TLC: Rf 0.24 (hexane-acetone (4:1)); R-2: pink.- $C_{14}H_{19}NO_5$ (281.3) Calcd. C 59.8 H 6.81 N 5.0 Found C 60.0 H 6.70 N 4.8.- IR (KBr): $\tilde{\nu}$max = 3445, 3324 (NH), 1667 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 213 (4.33), 259 (3.95), 304 (4.31); + HCl: 212 (4.16), 240 (4.01), 308 (4.16), 330 nm (sh, 4.05).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.20 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.40 (s, 3H, $OCH_2OC\underline{H}_3$), 3.82 (s, 3H, 4-OCH_3), 4.04 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 7.06 (d, 1H, J = 8 Hz, 5-H), 7.2 (br s, 1H, N-H), 7.27 (dd, 1H, J_1 = 8, J_2 = 2 Hz, 6-H), 7.30 (d, 1H, J = 2 Hz, 2-H), 8.0 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 55.7 and 55.8 ($OCH_2O\underline{C}H_3$ and 4-OCH_3), 57.8 ($O\underline{C}H_2CH_3$), 80.5 (C-α), 95.0 ($O\underline{C}H_2OCH_3$), 112.2 (C-5), 114.8 (C-2), 120.7 (C-6), 128.6 (C-1), 145.6 (C-3), 151.5 (C-4), 160.3 (C-β), 169.5 (-CO_2-).- MS: m/z (rel.Int. > 20%) = 281 (80, $M^{+\cdot}$), 236 (33), 203 (42), 191 (48), 190 (77), 175 (35), 174 (53), 162 (81), 146 (24), 45 (100).

β-Amino-2-bromo-4-(methoxymethyloxy)-5-methoxycinnamic acid ethyl ester (**2f**)

1. *2-Bromo-4-(methoxymethyloxy)-5-methoxybenzonitrile*

From 22.8 g (0.1 mol) crude 2-bromo-4-hydroxy-5-methoxybenzonitrile - prepared from 27.3 g (0.1 mol) 4-acetoxy-2-bromo-5-methoxybenzaldehyde[18] by a known procedure[19] - according to lit.[17]. Purification by MPLC on silica gel (CH_2Cl_2-hexane (4:1)).- Yield 14 g (51%); white needles.- Mp. 124-126°C (CH_2Cl_2-hexane).- TLC: Rf 0.41 (CH_2Cl_2).- $C_{10}H_{10}BrNO_3$ (272.1) Calcd. C 44.1 H 3.70 N 5.2 Found C 44.1 H 3.81 N 5.3.- IR (KBr): $\tilde{\nu}$max = 2229 cm^{-1} (CN).- UV: λmax (lg ε) = 222 (4.55), 255 (4.04), 296 (3.58), 304 nm (3.59).- ^{1}H-NMR: δ (ppm) = 3.51 (s, 3H, $OCH_2OC\underline{H}_3$), 3.89 (s, 3H, 5-OCH_3), 5.28 (s, 2H, $OC\underline{H}_2OCH_3$), 7.09 (s, 1H, 6-H), 7.40 (s, 1H, 3-H).- ^{13}C-NMR: δ (ppm) = 56.4 and 56.7 ($OCH_2O\underline{C}H_3$ and 5-OCH_3), 95.3 ($O\underline{C}H_2OCH_3$), 108.2 (C-1), 115.9 (C-6), 117.2 and 117.5 (C-2 and CN), 119.6 (C-3), 149.0 and 150.8 (C-4 and C-5).- MS: m/z (rel.Int.) = 273 (2, $M_1^{+\cdot}$), 271 (2, $M_2^{+\cdot}$), 45 (100).

2. *β-Amino-2-bromo-4-(methoxymethyloxy)-5-methoxycinnamic acid ethyl ester* (**2f**)

From 5.44 g (20 mmol) 2-bromo-4-(methoxymethyloxy)-5-methoxybenzonitrile as described for **2a**. Purification by MPLC on silica gel (hexane-acetone (4:1)).- Yield 2.21 g (31%); colourless gum.- TLC: Rf 0.20 (hexane-acetone (4:1)); R-2: pink.- IR: $\tilde{\nu}$max = 3502, 3335 (NH), 1663 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 207 (4.49), 287 (3.79); + HCl: 207 (4.47), 287 nm (4.27).- ^{1}H-NMR ([D$_6$]DMSO): δ (ppm) = 1.19 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.39 (s, 3H, $OCH_2OC\underline{H}_3$), 4.04 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.37 (s, 1H, α-H), 5.21 (s, 2H, $OC\underline{H}_2OCH_3$), 6.99 (s, 1H, 6-H), 7.18 (br s, 1H, N-H), 7.30 (s, 1H, 3-H), 7.92 (br s, 1H, N-H).- ^{13}C-NMR ([D$_6$]DMSO): δ (ppm) = 14.5 ($OCH_2\underline{C}H_3$), 55.87 and 55.92 ($OCH_2O\underline{C}H_3$ and 3-OCH_3), 58.0 ($O\underline{C}H_2CH_3$), 83.9 (C-α), 94.7 ($O\underline{C}H_2OCH_3$), 110.1, 113.6 and 120.0 (C-6, C-2 and C-3), 132.4 (C-1), 146.7 and 148.9 (C-4 and C-5), 160.4 (C-β), 168.9 (-CO_2-).- MS: m/z (rel.Int.) = 361.0353 (calcd. for $C_{14}H_{18}{}^{81}BrNO_5$: 361.0349) (0.8, $M_1^{+\cdot}$), 359.0370 (calcd. for $C_{14}H_{18}{}^{79}BrNO_5$: 359.0369) (0.8, $M_2^{+\cdot}$), 280.1187 (calcd. for $C_{14}H_{18}NO_5$: 280.1185) (49), 252 (19), 236 (12), 222 (18), 208 (17), 206 (14), 190 (14), 45 (100), 43 (17).

5-Methoxy-4-methyl-2-phenylnicotinic acid ethyl ester (**4a**)

191 mg (1 mmol) **2a**, 270 mg (2 mmol) **3**, 0.4 g (ca. 4 mmol) triethylamine and 0.1 ml conc. HCl (ca. 1 mmol HCl) were added successively to 5-10 ml EtOH and refluxed for 2-3 h. To remove triethylamine, 50 ml H_2O were added, the mixture was adjusted to pH 5-6 with 2N HCl and then extracted with ether (3 x 20 ml). The org. layers were dried, evaporated *in vacuo* and purified by MPLC on silica gel (CH_2Cl_2-acetone (49:1)).- Yield 244 mg (90%); colourless solid.- Mp. 68-70°C (MeOH).- TLC: Rf 0.35 ($CHCl_3$-acetone (9:1)); R-3: orange-red.- $C_{16}H_{17}NO_3$ (271.3) Calcd. C 70.8 H 6.27 N 5.2 Found C 70.8 H 6.39 N 5.1.- IR: $\tilde{\nu}$max = 1726 cm^{-1} (CO).- UV: λmax (lg ε) = 204 (4.58), 249 (4.23), 281 (3.89); + HCl: 204 (4.51), 247 (4.23), 297 nm (3.95).- ^{1}H-NMR: δ (ppm) = 1.03 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.28 (s, 3H, 4-CH_3), 3.97 (s, 3H, 5-OCH_3), 4.13 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 7.57-7.34 (m, 5H, 2'-H to 6'-H), 8.29 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.5 (4-CH_3), 13.6 ($OCH_2\underline{C}H_3$), 56.3 (5-OCH_3), 61.4 ($O\underline{C}H_2CH_3$), 128.06, 128.09, 128.16 (C-2' to C-6'), 129.9 (C-3), 132.5 (C-6), 133.8 (C-4), 139.9 (C-1'), 149.3 (C-2), 152.7 (C-5), 168.2 (-CO_2-).- MS: m/z (rel.Int.) = 271 (68, $M^{+\cdot}$), 243 (15), 242 (100), 227 (14), 226 (37), 199 (50), 198 (15), 183 (26), 182 (18), 156 (20), 155 (11), 154 (16), 129 (12), 128 (31), 127 (24), 83 (11), 77 (11).

5-Methoxy-6-methyl-2-phenylnicotinic acid ethyl ester (**5**)

As described for **4a**, but pyridine was used instead of triethylamine. After 3 h the solvents were evaporated without extraction procedure. Purification by MPLC on silica gel (CH_2Cl_2-acetone (99:1)).- Yield 122 mg (45%); colourless crystals.- Mp. 73-75°C (MeOH).- TLC: Rf 0.55 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{16}H_{17}NO_3$ (271.3) Calcd. C 70.8 H 6.27 N 5.2 Found C 70.9 H 5.99 N 4.9.- IR: $\tilde{\nu}$max = 1713 cm^{-1} (CO).- UV: λmax (lg ε) = 204 (4.51), 258 (4.13), 288 (3.91); + HCl: 203 (4.49), 258 (4.15), 299 nm (3.93).- ^{1}H-NMR: δ (ppm) = 1.00 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.55 (s, 3H, 6-CH_3), 3.92 (s, 3H, 5-OCH_3), 4.11 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 7.34-7.42 (m, 3H, 3'-H, 4'-H, 5'-H), 7.48-7.44 (m, 2H, 2'-H, 6'-H), 7.50 (s, 1H, 4-H).- ^{13}C-NMR: δ (ppm) = 13.6 ($OCH_2\underline{C}H_3$), 19.7 (6-CH_3), 55.6 (5-OCH_3), 61.3 ($O\underline{C}H_2CH_3$), 117.5 (C-4), 125.0 (C-3), 127.8 (C-4'), 127.9 (C-2', C-6'), 128.6 (C-3', C-5'), 140.5 (C-1'), 150.2 (C-6), 151.4 (C-2), 152.4 (C-5), 168.2 (-CO_2-).- MS: m/z (rel.Int.) = 271 (56, $M^{+\cdot}$), 243 (15), 242 (100), 227 (13), 226 (15), 199 (33), 184 (9), 183 (23), 156 (14), 115 (21), 114 (20), 83 (12).

5-Methoxy-2-(4-methoxyphenyl)-4-methylnicotonic acid ethyl ester (**4b**)

From 1.105 g (5 mmol) **2b** as described for **4a**. Purification by MPLC on silica gel ($CHCl_3$-acetone (49:1)).- Yield 1.37 g (91%); colourless solid.- Mp. 55-57°C (MeOH).- TLC: Rf 0.34 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{17}H_{19}NO_4$ (301.3) Calcd. C 67.7 H 6.31 N 4.7 Found C 67.7 H 6.55 N 4.9.- IR (KBr): $\tilde{\nu}$max = 1732 cm^{-1} (CO).- UV: λmax (lg ε) = 205 (4.62), 261 (4.30), 286 (sh, 4.12); + HCl: 205 (4.48), 269 (4.22), 319 nm (3.98).- ^{1}H-NMR: δ (ppm) = 1.10 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.26 (s, 3H, 4-CH_3), 3.83 (s, 3H, 4'-OCH_3), 3.96 (s, 3H, 5-OCH_3), 4.18 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 6.93 (**AA'BB'**, 2H, 3'-H, 5'-H), 7.50 (**AA'BB'**, 2H, 2'-H, 6'-H), 8.26 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.5 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 55.3 (4'-OCH_3), 56.3 (5-OCH_3), 61.4 ($O\underline{C}H_2CH_3$), 113.7 (C-3', C-5'), 129.4 (C-2', C-6'), 129.7 (C-3), 132.4 (C-1' and C-6), 133.9 (C-4), 148.8 (C-2), 152.5 (C-5), 159.7 (C-4'), 168.4 (-CO_2-).- MS: m/z (rel.Int.) = 301 (100, $M^{+\cdot}$), 273 (13), 272 (78), 256 (23), 214 (12), 186 (16), 115 (13), 58 (23), 43 (68), 40 (13).

2-(4-Hydroxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester (**4c**)

1. *5-Methoxy-2-[4-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester*

From 502 mg (2 mmol) **2c** as described for **4a**. Purification by MPLC (CH_2Cl_2-acetone (24:1)).- Yield 628 mg (95%); viscous oil.- TLC: Rf 0.34 (CH_2Cl_2-acetone (9:1)); R-3: positive.- $C_{18}H_{21}NO_5$ (331.4) Calcd. C 65.2 H 6.39 N 4.2 Found C 65.0 H 6.07 N 4.3.- IR: $\tilde{\nu}$max = 1723 cm^{-1} (CO).- UV: λmax (lg ε) = 204 (4.48), 259 (4.17), 287 (sh, 3.92); + HCl: 204 (4.32), 264 (4.10), 313 nm (3.80).- ^{1}H-NMR: δ (ppm) = 1.10 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.26 (s, 3H, 4-CH_3), 3.48 (s, 3H, $OCH_2OC\underline{H}_3$), 3.97 (s, 3H, 5-OCH_3), 4.19 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 5.20 (s, 2H, $OC\underline{H}_2OCH_3$), 7.06 (**AA'BB'**, 2H, 3'-H, 5'-H), 7.49 (**AA'BB'**, 2H, 2'-H, 6'-H), 8.27 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.6 (4-CH_3), 13.7 ($OCH_2\underline{C}H_3$), 55.9 ($OCH_2O\underline{C}H_3$), 56.3 (5-OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 94.4 ($O\underline{C}H_2OCH_3$), 116.0 (C-3', C-5'), 129.4 (C-2', C-6'), 129.8 (C-3), 132.4 (C-6), 133.4 (C-1'), 133.9 (C-4), 148.7 (C-2), 152.6 (C-5), 157.3 (C-4'), 168.4 (-CO_2-).- MS: m/z (rel.Int.) = 331 (73, $M^{+\cdot}$), 270 (35), 45 (100).

2. *2-(4-Hydroxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester* (**4c**)

From 331 mg (1 mmol) 5-methoxy-2-[4-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester by refluxing in 10 ml EtOH containing 0.2 ml conc. HCl for 2-3 h. The solution was concentrated to 2 ml, H_2O (50 ml) was added and then $NaHCO_3$-solution for neutralization; subsequently the title compound was extracted with ether.- Yield 275 mg (96%); white needles.- Mp. 170-173°C (MeOH).- TLC: Rf 0.17 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{16}H_{17}NO_4$ (287.3) Calcd. C 66.9 H 5.96 N 4.9 Found C 67.0 H 5.80 N 4.9.- IR (KBr): $\tilde{\nu}$max = 3400 (OH), 1732 cm^{-1} (CO).- UV (EtOH): λmax (lg ε) = 204 (4.55), 263 (4.20), 287 (sh, 4.05); + HCl: 206 (4.42), 270 (4.12), 325 (3.81); + NaOH: 302 nm (4.27).- ^{1}H-NMR: δ (ppm) = 1.09 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.26 (s, 3H, 4-CH_3), 3.95 (s, 3H, 5-OCH_3), 4.17 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 6.62 (**AA'BB'**, 2H, 3'-H, 5'-H), 7.29 (**AA'BB'**, 2H, 2'-H, 6'-H), 8.22 (s, 1H, 6-H), 8.52 (br s, 1H, 4'-OH).- ^{13}C-NMR: δ (ppm) = 12.7 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 56.4 (5-OCH_3), 61.6 ($O\underline{C}H_2CH_3$), 115.6 (C-3', C-5'), 129.5 (C-2', C-6'), 130.3 and 130.7 (C-3 and C-1'), 131.6 (C-6), 134.6 (C-4), 149.1 (C-2), 152.8 (C-5), 157.1 (C-4'), 168.3 (-CO_2-).- MS: m/z (rel.Int.) = 287 (73, $M^{+\cdot}$), 259 (14), 258 (100), 243 (14), 242 (41), 215 (15), 198 (11), 115 (13).

2-(4-Hydroxy-3-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester (**4d**)

1. *5-Methoxy-2-[3-methoxy-4-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester*

From 562 mg (2 mmol) **2d** as described for **4a**. Purification by MPLC on silica gel (CH_2Cl_2-acetone (47:3)).- Yield 671 mg (93%); crystals.- Mp. 75-77°C (MeOH).- TLC: Rf 0.34 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{19}H_{23}NO_6$ (361.4) Calcd. C 63.1 H 6.41 N 3.9 Found C 63.1 H 6.28 N 3.9.- IR (KBr): $\tilde{\nu}$max = 1712 cm^{-1} (CO).- UV: λmax (lg ε) = 206 (4.50), 258 (4.11), 287 (4.00); + HCl: 215 (4.06), 266 (4.03), 280 (sh, 3.93), 323 nm (3.82).- ^{1}H-NMR: δ (ppm) = 1.10 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.26 (s, 3H, 4-CH_3), 3.52 (s, 3H, $OCH_2OC\underline{H}_3$), 3.91 (s, 3H, 3'-OCH_3), 3.97 (s, 3H, 5-OCH_3), 4.18 (q, J = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5.25 (s, 2H, $OC\underline{H}_2OCH_3$), 7.05 (dd, 1H, J_1 = 8, J_2 = 2 Hz, 6'-H), 7.14 (d, 1H, J = 8 Hz, 5'-H), 7.22 (d, 1H, J = 2 Hz, 2'-H), 8.29 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.6 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 55.9 ($OCH_2O\underline{C}H_3$), 56.1 (3'-OCH_3), 56.6 (5-OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 95.5 ($O\underline{C}H_2OCH_3$), 112.0 (C-2'), 115.9 (C-5'), 120.7 (C-6'), 130.0 (C-3), 132.4 (C-6), 134.0 and 134.4 (C-4 and C-1'), 146.7 (C-4'), 148.7 (C-2), 149.5 (C-3'), 152.7 (C-5), 168.4 (-CO_2-).- MS: m/z (rel.Int.) = 361 (58, $M^{+\cdot}$), 316 (25), 302 (11), 299 (19), 288 (15), 271 (17), 270 (100), 243 (13), 242 (66), 228 (16), 226 (16), 45 (81).

2. *2-(4-Hydroxy-3-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester* (**4d**)

From 361 mg (1 mmol) 5-methoxy-2-[3-methoxy-4-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester as described for **4c**.- Yield 303 mg (96%); beige crystals.- Mp. 275-278°C (MeOH).- TLC: Rf 0.15 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{17}H_{19}NO_5$ (317.3) Calcd. C 64.3 H 6.03 N 4.4 Found C 64.2 H 5.89 N 4.4.- IR (KBr): $\tilde{\nu}$max = 3400 (OH), 1733 cm^{-1} (CO).- UV: λmax (lg ε) = 207 (4.50), 266 (4.07), 291 (3.98); + HCl: 207 (4.36), 275 (4.03), 332 (3.83); + NaOH: 311 nm (4.15).- ^{1}H-NMR: δ (ppm) = 1.12 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.25 (s, 3H, 4-CH_3), 3.92 (s, 3H, 3'-OCH_3), 3.97 (s, 3H, 5-OCH_3), 4.18 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 5.79 (br s, 1H, 4'-OH), 6.91 (d, 1H, J = 8 Hz, 5'-H), 7.03 (dd, 1H, J_1 = 8, J_2 = 2 Hz, 6'-H), 7.15 (d, 1H, J = 2 Hz, 2'-H), 8.26 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.6 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 55.9 (3'-OCH_3), 56.3 (5-OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 111.0 (C-2'), 114.1 (C-5'), 121.3 (C-6'), 129.8 (C-3), 132.2 (C-1'), 132.3 (C-6), 133.9 (C-4), 145.9 and 146.5 (C-4' and C-3'), 148.9 (C-2), 152.6 (C-5), 168.5 (-CO_2-).- MS: m/z (rel.Int.) = 317 (100, $M^{+\cdot}$), 316 (18), 289 (12), 288 (75), 273 (12), 272 (18), 244 (17), 242 (11), 240 (14).

2-(3-Hydroxy-4-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester (**4e**)

1. *5-Methoxy-2-[4-methoxy-3-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester*

From 562 mg (2 mmol) **2e** as described for **4a**. Purification by MPLC on silica gel ($CHCl_3$).- Yield 640 mg (89%); crystals.- Mp. 70-72°C (MeOH).- TLC: Rf 0.16 ($CHCl_3$); R-3: positive.- $C_{19}H_{23}NO_6$ (361.4) Calcd. C 63.1 H 6.41 N 3.9 Found C 63.0 H 6.61 N 4.0.- IR: $\tilde{\nu}$max = 1723 cm^{-1} (CO).- UV: λmax (lg ε) = 207 (4.52), 262 (4.15), 286 (sh, 4.05); + HCl: 210 (4.40), 270 (4.08), 323 nm (3.87).- ^{1}H-NMR: δ (ppm) = 1.13 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 2.26 (s, 3H, 4-CH_3), 3.52 (s, 3H, $OCH_2OC\underline{H}_3$), 3.90 (s, 3H, 4'-OCH_3), 3.96 (s, 3H, 5-OCH_3), 4.20 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 5.25 (s, 2H, $OC\underline{H}_2OCH_3$), 6.92 (d, 1H, J = 8.5 Hz, 5'-H), 7.20 (dd, 1H, J_1 = 8.5, J_2 = 2 Hz, 6'-H), 7.39 (d, 1H, J = 2 Hz, 2'-H), 8.27 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.6 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 56.0 (4'-OCH_3), 56.2 ($OCH_2O\underline{C}H_3$), 56.4 (5-OCH_3), 61.5 ($O\underline{C}H_2CH_3$), 95.6 ($O\underline{C}H_2OCH_3$), 111.4 (C-5'), 116.6 (C-2'), 122.4 (C-6'), 129.9 (C-3), 132.1 (C-6), 132.5 (C-1'), 134.2 (C-4), 146.3 (C-3'), 148.4 (C-2), 150.0 (C-4'), 152.6 (C-5), 166.3 (-CO_2-).- MS: m/z (rel.Int.) = 361 (38, $M^{+\cdot}$), 316 (59), 300 (17), 288 (26), 272 (11), 271 (11), 270 (17), 243 (11), 242 (44), 228 (20), 227 (19), 214 (12), 200 (11), 199 (14), 45 (100).

2. *2-(3-Hydroxy-4-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester* (**4e**)

From 361 mg (1 mmol) 5-methoxy-2-[4-methoxy-3-(methoxymethyloxy)phenyl]-4-methylnicotinic acid ethyl ester as described for **4c**. Purification by MPLC on silica gel ($CHCl_3$-acetone (9:1)).- Yield 285 mg (90%); beige crystals.- Mp. 107-109°C (MeOH).- TLC: Rf 0.18 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{17}H_{19}NO_5$ (317.3) Calcd. C 64.3 H 6.03 N

4.4 Found C 64.4 H 6.22 N 4.4.- IR (KBr): $\tilde{\nu}$max = 3499 (OH), 1713 cm^{-1} (CO).- UV: λmax (lg ε) = 207 (4.54), 263 (4.10), 291 (4.06); + HCl: 207 (4.50), 213 (sh, 4.42), 275 (4.07), 329 (3.86); + NaOH: 242 (4.36), 274 (3.99), 305 nm (3.88).- ^{1}H-NMR: δ (ppm) = 1.14 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.26 (s, 3H, 4-CH_3), 3.90 (s, 3H, 4'-OCH_3), 3.97 (s, 3H, 5-OCH_3), 4.22 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$), 6.86 (d, 1H, J = 8 Hz, 5'-H), 7.06 (dd, 1H, J_1 = 8, J_2 = 2 Hz, 6'-H), 7.17 (d, 1H, J = 2 Hz, 2'-H), 8.26 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.6 (4-CH_3), 13.8 ($OCH_2\underline{C}H_3$), 56.0 (4'-OCH_3), 56.4 (5-OCH_3), 61.6 ($O\underline{C}H_2CH_3$), 110.4 (C-5'), 114.7 (C-2'), 120.3 (C-6'), 130.0 (C-3), 131.9 (C-6), 132.8 (C-1'), 134.3 (C-4), 145.6 (C-3'), 147.0 (C-4'), 148.5 (C-2), 152.7 (C-5), 168.2 (-CO_2-).- MS: m/z (rel.Int.) = 317 (88, $M^{+\cdot}$), 289 (16), 288 (100), 274 (13), 273 (25), 272 (32), 245 (17), 230 (25), 228 (19), 212 (12), 202 (15), 159 (13).

2-(2-Bromo-4-hydroxy-5-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester (**4f**)

1. *2-[2-Bromo-5-methoxy-4-(methoxymethyloxy)phenyl]-5-methoxy-4-methylnicotinic acid ethyl ester*

From 1.08 g (3 mmol) **2f** as described for **4a**. Purification by MPLC on silica gel (CH_2Cl_2-acetone (49:1 → 9:1)).- Yield 0.63 g (48%); pale yellow solid.- Mp. 43-46°C (MeOH).- TLC: Rf 0.25 (CH_2Cl_2-acetone (19:1)); R-3: positive.- $C_{19}H_{22}BrNO_6$ (440.3) Calcd. C 51.8 H 5.04 N 3.2 Found C 52.1 H 5.27 N 3.3.- IR: $\tilde{\nu}$max = 1723 cm^{-1} (CO).- UV: λmax (lg ε) = 208 (4.60), 230 (sh, 4.24), 283 (3.96); + HCl: 209 (4.52), 235 (sh, 4.24), 287 (3.91), 350 nm (sh, 3.19).- ^{1}H-NMR: δ (ppm) = 1.01 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.30 (s, 3H, 4-CH_3), 3.51 (s, 3H, $OCH_2O\underline{CH_3}$), 3.82 (s, 3H, 5'-OCH_3), 3.99 (s, 3H, 5-OCH_3), 4.09 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$), 5.23 (s, 2H, $O\underline{CH_2}OCH_3$), 6.84 (s, 1H, 6'-H), 7.39 (s, 1H, 3'-H), 8.29 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.8 (4-CH_3), 13.6 ($OCH_2\underline{C}H_3$), 56.1, 56.2 and 56.3 ($OCH_2O\underline{C}H_3$, 5'-OCH_3 and 5-OCH_3), 61.3 ($O\underline{C}H_2CH_3$), 95.6 ($O\underline{C}H_2OCH_3$), 113.2 (C-2'), 113.9 (C-6'), 120.2 (C-3'), 130.6 (C-3), 132.2 (C-6), 134.1 (C-4), 134.4 (C-1'), 146.8, 148.6 and 149.0 (C-4', C-2 and C-5'), 153.1 (C-5), 167.1 (-CO_2-).- MS: m/z (rel.Int.) = 441 (2, $M_1^{+\cdot}$), 439 (2, $M_2^{+\cdot}$), 361 (16), 360 (78), 332 (20), 270 (13), 269 (14), 45 (100).

2. *2-(2-Bromo-4-hydroxy-5-methoxyphenyl)-5-methoxy-4-methylnicotinic acid ethyl ester* (**4f**)

From 440 mg (1 mmol) 2-[2-bromo-4-(methoxymethyloxy)-5-methoxyphenyl]-5-methoxy-4-methylnicotinic acid ethyl ester as described for **4c**.- Yield 375 mg (95%); beige crystals.- Mp. 174-177°C (MeOH).- TLC: Rf 0.40 ($CHCl_3$-acetone (9:1)); R-3: positive.- $C_{17}H_{18}BrNO_5$ (396.2) Calcd. C 51.5 H 4.58 N 3.5 Found C 51.3 H 4.81 N 3.7.- IR: $\tilde{\nu}$max = 3538 (OH), 1723 cm^{-1} (CO).- UV: λmax (lg ε) = 206 (4.57), 228 (sh, 4.24), 286 (3.83); + HCl: 208 (4.50), 237 (sh, 4.13), 285 (3.90), 325 (sh, 3.33); + NaOH: 237 (4.13), 285 (3.91), 305 nm (sh, 3.83).- ^{1}H-NMR: δ (ppm) = 1.02 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 2.30 (s, 3H, 4-CH_3), 3.83 (s, 3H, 5'-OCH_3), 3.99 (s, 3H, 5-OCH_3), 4.09 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$), 6.78 (s, 1H, 6'-H), 7.13 (s, 1H, 3'-H), 8.28 (s, 1H, 6-H).- ^{13}C-NMR: δ (ppm) = 12.8 (4-CH_3), 13.7 ($OCH_2\underline{C}H_3$), 55.1 (5'-OCH_3), 56.3 (5-OCH_3), 61.4 ($O\underline{C}H_2CH_3$), 112.9 (C-6'), 113.8 (C-2'), 118.6 (C-3'), 130.9 (C-3), 132.0 (C-6), 134.2 (C-4 and C-1'), 145.7 and 146.3 (C-4' and C-5'), 149.1 (C-2), 153.2 (C-5), 167.2 (-CO_2-).- MS: m/z (rel.Int.) = 397 (3, $M_1^{+\cdot}$), 395 (3, $M_2^{+\cdot}$), 317 (17), 316 (91), 289 (13), 288 (85), 287 (13), 272 (13), 244 (11), 229 (20), 228 (100), 216 (10), 58 (15).

Onychine (**1**, *all R = H) via 2-Phenyl-4-methylnicotinic acid ethyl ester*

1. *3-Chlorocrotonaldehyde*

From 2.9 g (0.05 mol) acetone according to lit.[8]. The product is a mixture containing 60% of the *Z*- and 40% of the *E*-isomer.- Yield 2.01 g (39%); pale yellow liquid.-TLC: Rf 0.42 (hexane-$CHCl_3$ (1:1)); R-1: positive.- IR: $\tilde{\nu}$max = 1686, 1677 cm^{-1} (α,β-unsaturated CO).- UV: λmax (lg ε) = 203 (3.04), 240 nm (3.31).- ^{1}H-NMR: δ (ppm), signals for *Z*-isomer: 2.36 (d, 3H, J = 1.2 Hz, CH_3), 6.11 (dq, 1H, J_1 = 7, J_2 = 1.2 Hz, 2-H), 10.00 (d, 1H, J = 7 Hz, 1-H).- Signals for *E*-isomer: 2.58 (d, 3H, J = 1.2 Hz, CH_3), 6.28 (dq, 1H, J_1 = 7, J_2 = 1.2 Hz, 2-H), 9.84 (d, 1H, J = 7 Hz, 1-H).- ^{13}C-NMR: δ (ppm), signals for *Z*-isomer: 27.9 (C-4), 126.6 (C-2), 153.4 (C-3), 191.2 (C-1).- Signals for *E*-isomer: 22.7 (C-4), 129.6 (C-2), 157.2 (C-3), 187.8 (C-1).- MS: m/z (rel.Int.) = 106 (32, $M_1^{+\cdot}$), 104 (100, $M_2^{+\cdot}$), 105 (21), 103 (49), 75 (14), 73 (28), 69 (21).

2. *2-Phenyl-4-methylnicotinic acid ethyl ester*

From 573 mg (3 mmol) **2a** and 630 mg (6 mmol) 3-chlorocrotonaldehyde as described for **4a**. Purification by MPLC on silica gel (hexane-$CHCl_3$ (4:1)).- Yield 290 mg (54%); yellow oil.- TLC: Rf 0.41 ($CHCl_3$-acetone (49:1)).- ^{1}H-NMR and MS are in agreement with published data[20]. 2-Phenyl-4-methylnicotinic acid ester was converted to onychine according to lit.[20].

3. *Onychine*

The physicochemical properties of the product agree with the published data (lit.[2,20,21]).

2-Methoxyonychine (**1a**)

271 mg (1 mmol) **4a** were stirred in polyphosphoric acid at 140°C for 3-5 h according to lit.[20]. Purification on LiChroprep® RP 18 (MeOH-H_2O (4:1 → 9:1)).- Yield 207 mg (92%); yellow needles.- Mp. 163-165°C ($CHCl_3$).- TLC: Rf 0.35 (CH_2Cl_2-acetone (9:1)).- $C_{14}H_{11}NO_2 \cdot 0.5$ MeOH (241.3) Calcd. C 72.2 H 5.43 N 5.8 Found C 72.2 H 5.60 N 5.9.- IR (KBr): $\tilde{\nu}$max = 1704 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 213 (4.26), 249 (4.33), 270 (4.40), 298 (3.79), 311 (3.70), 324 (3.47); + HCl: additional λmax at 338 nm (3.26).- ^{1}H-NMR: δ (ppm) = 2.53 (s, 3H, CH_3), 3.95 (s, 3H, 2-OCH_3), 7.34 (ddd, 1H, $J_1 = J_2$ = 7.3, J_3 = 1 Hz, 7-H), 7.54 (ddd, 1H, $J_1 = J_2$ = 7.3, J_3 = 1 Hz, 6-H), 7.65 (ddd, 1H, J_1 = 7.3, $J_2 = J_3$ = 1 Hz, 8-H), 7.74 (ddd, 1H, J_1 = 7.3, $J_2 = J_3$ = 1 Hz, 5-H), 8.05 (s, 1H, 3-H).- ^{13}C-NMR: δ (ppm) = 10.1 (CH_3), 56.5 (2-OCH_3), 120.0 (C-5), 123.7 (C-8), 126.8 (C-9a), 129.7 (C-7), 134.3 (C-3), 135.1 (C-6), 135.5 (C-8a), 137.4 (C-1), 143.3 (C-4b), 155.0 (C-2), 157.5 (C-4a), 193.2 (C-9).- MS: m/z (rel.Int.) = 225 (50, $M^{+\cdot}$), 207 (12), 196 (26), 195 (15), 183 (15), 182 (100), 127 (37), 126 (17), 83 (18), 77 (13), 63 (12).

2,7-Dimethoxyonychine (**1b**)

From 301 mg (1 mmol) **4b** as described for **1a**. Purification by MPLC on LiChroprep® RP 18 (MeOH-H_2O (4:1)).- Yield 148 mg (58%); orange crystals.- Mp. 204-206°C (MeOH).- TLC: Rf 0.12 ($CHCl_3$).- $C_{15}H_{13}NO_3 \cdot 0.5$ MeOH (271.3) Calcd. C 69.6 H 5.35 N 5.3 Found C 69.6 H 5.37 N 5.3.- IR, UV/VIS, ^{1}H-NMR, ^{13}C-NMR, MS are identical with those of an authentic sample[1].

2,7-Dihydroxyonychine (**1g**)

50 mg **1b** were refluxed overnight in 20 ml of a mixture (1:1) of HBr (48%) and acetic acid. After addition of water, the mixture was neutralized with $NaHCO_3$ and extracted with ether. Purification by MPLC on silica gel ($CHCl_3$-MeOH (19:1)) yielded 39 mg (88%) **1g** besides traces of **1c** as orange-yellow crystals (MeOH).- Mp. > 300°C ($CHCl_3$-MeOH).- TLC: Rf 0.51 ($CHCl_3$-MeOH (9:1)).- HR-MS: 227.0583 (calcd. for $C_{13}H_9NO_3$: 227.0582) (100, $M^{+\cdot}$).- IR, UV/VIS, ^{1}H-NMR, ^{13}C-NMR, MS identical with an authentic sample isolated from *Piptostigma fugax*[1].

7-Hydroxy-2-methoxyonychine (**1c**)

287 mg (1 mmol) **4c** were stirred in 30 ml of polyphosphoric acid at 130° for 3 h. The mixture was poured in 500 ml H_2O and kept boiling for 60 min. Neutralization with NH_3, extraction with CH_2Cl_2 and subsequent purification by MPLC on silica gel RP 18 (MeOH-H_2O (3:1)) yielded 72 mg (30%) **1c** as a yellow-orange solid.- Mp. > 300°C (MeOH).- TLC: Rf

0.75 ($CHCl_3$-MeOH (19:1)).- $C_{14}H_{11}NO_3$ · MeOH (273.3) Calcd. C 65.9 H 5.48 N 5.1 Found C 66.2 H 5.32 N 5.3.- IR, UV/VIS, ^{1}H-NMR, ^{13}C-NMR and MS are identical with an authentic sample isolated from *Piptostigma fugax*[1].

7-Hydroxy-2,6-dimethoxyonychine (**1d**)

From 254 mg (0.8 mmol) **4d** as described for **1c**. Separation by MPLC on silica gel (CH_2Cl_2-MeOH (19:1 → 9:1)) gave **1d** (major compound) and **1d'** (minor compound).-

1d: Yield 40 mg (18%); orange-red needles.- Mp. 193-195°C ($CHCl_3$-MeOH).- TLC: Rf 0.40 (CH_2Cl_2-MeOH (9:1)).- $C_{15}H_{13}NO_4$ · MeOH (303.3) Calcd. C 63.4 H 5.64 N 4.6 Found C 63.0 H 5.60 N 4.8.- IR (KBr): $\tilde{\nu}$max = 3470 (OH), 1698 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 221 (4.12), 227 (4.10), 253 (4.27), 266 (sh, 4.24), 295 (4.40), 332 (3.77), 344 (sh, 3.69); + HCl: 242 (sh, 4.25), 253 (4.27), 307 (sh, 4.19), 318 (4.22), 376 (4.04); + NaOH: 236 (4.09), 287 (4.30), 314 (4.30), 369 nm (3.99).- ^{1}H-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 2.48 (s, 3H, CH_3), 3.95 (s, 3H, 2-OCH_3), 4.03 (s, 3H, 6-OCH_3), 7.10 (s, 1H, 8-H), 7.31 (s, 1H, 5-H), 7.87 (s, 1H, 3-H).- ^{13}C-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 10.1 (CH_3), 56.6 and 56.9 (2-OCH_3 and 6-OCH_3), 104.5 (C-5), 111.5 (C-8), 128.4 (C-9a), 130.0 (C-8a), 131.6 (C-3), 136.2 (C-4b), 139.7 (C-1), 149.6 (C-7), 154.8 and 155.9 (C-6 and C-2), 157.5 (C-4a), 192.4 (C-9).- MS: m/z (rel.Int.) = 271 (100, $M^{+\cdot}$), 256 (54), 228 (58), 213 (17).

6,7-Dihydroxy-2-methoxyonychine (**1d'**)

Minor by-product of the synthesis of **1d**.- Yield 26 mg (12%); orange-red needles.- Mp. > 280°C ($CHCl_3$-MeOH).- TLC: Rf 0.18 (CH_2Cl_2-MeOH (9:1)).- $C_{14}H_{11}NO_4$ · 0.5 MeOH (273.3) Calcd. C 63.7 H 4.79 N 5.1 Found C 63.7 H 4.72 N 5.3.- IR (KBr): $\tilde{\nu}$max = 3390 (OH), 1698 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 203 (4.39), 223 (4.40), 228 (4.40), 252 (4.54), 266 (sh, 4.38), 300 (4.66), 334 (4.07), 353 (3.90); + HCl: 231 (sh, 4.33), 242 (sh, 4.44), 254 (4.49), 308 (4.46), 319 (4.45), 380 (4.14); + NaOH: 210 (4.84), 228 (4.43), 256 (4.47), 329 (4.59), 370 (sh, 4.11), 494 nm (3.94).- ^{1}H-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 2.47 (s, 3H, CH_3), 3.94 (s, 3H, 2-OCH_3), 7.08 (s, 1H, 8-H), 7.13 (s, 1H, 5-H), 7.83 (s, 1H, 3-H).- ^{13}C-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 10.0 (CH_3), 56.9 (2-OCH_3), 107.9 (C-5), 111.5 (C-8), 128.3 and 128.7 (C-9a and C-8a), 132.4 (C-3), 137.5 (C-4b), 138.2 (C-1), 147.6 (C-7), 153.2 (C-6), 155.4 (C-2), 158.0 (C-4a), 193.1 (C-9).- MS: m/z (rel.Int.) = 257 (100, $M^{+\cdot}$), 242 (36), 228 (12), 214 (85), 158 (69), 129 (11).

6-Hydroxy-2,7-dimethoxyonychine (**1e**) *(Oxylopidine*[11]*)*

From 254 mg (0.8 mmol) **4e** as described for **1c**. Purification by MPLC ($CHCl_3$-MeOH (19:1)).- Yield 31 mg (14%); orange-yellow crystals.- Mp. 288-290°C (MeOH).- TLC: Rf 0.37 ($CHCl_3$-MeOH (9:1)).- $C_{15}H_{13}NO_4$ · 0.5 MeOH (287.3) Calcd. C 64.8 H 5.26 N 4.9 Found 64.8 H 5.44 N 5.0.- IR (KBr): $\tilde{\nu}$max = 3529 (OH), 1703 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 205 (4.27), 222 (4.28), 252 (4.44), 265 (sh, 4.27), 301 (4.51), 334 (4.09), 386 (sh, 3.31), 465 (3.16); + HCl: 210 (4.21), 220 (4.22), 229 (4.20), 252 (4.44), 304 (4.45), 322 (sh, 4.26), 352 (sh, 3.86), 377 (3.88), 440 (sh, 3.15); + NaOH: 254 (4.43), 268 (sh, 4.32), 333 (4.51), 366 (sh, 3.98), 383 (sh, 3.88), 489 nm (3.74).- ^{1}H-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 2.49 (s, 3H, CH_3), 3.94 and 3.95 (2 x s, 3H, 2-OCH_3, 7-OCH_3), 7.20 and 7.21 (2 x s, 1H, 8-H and 5-H), 7.88 (s, 1H, 3-H).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 9.2 (CH_3), 55.9 (7-OCH_3), 56.5 (2-OCH_3), 106.8 and 107.6 (C-8 and C-5), 126.3 and 126.5 (C-9a and C-8a), 133.9 (C-4b), 135.0 (C-3), 137.9 (C-1), 148.9 (C-7), 153.6 (C-6), 154.0 (C-2), 156.2 (C-4a), 191.0 (C-9).- MS: m/z (rel.Int.) = 271 (89, $M^{+\cdot}$), 257 (13), 256 (100), 228 (55), 213 (23), 185 (15).

5-Bromo-7-hydroxy-2,8-dimethoxyonychine (5-Bromo- **1f**)

From 230 mg **4f** as described for **1c**. The two products of this reaction were separated by liquid extraction from CH_2Cl_2-solution. The more polar 5-bromo-7,8-dihydroxy-2-methoxyonychine was extracted with $NaHCO_3$-solution. The remaining CH_2Cl_2-layer was purified by MPLC on silica gel ($CHCl_3$-acetone (19:1)).- Yield 28 mg (13%); orange-red crystals.- Mp. 238-241°C ($CHCl_3$).- TLC: Rf 0.53 ($CHCl_3$-acetone (9:1)).- $C_{15}H_{12}BrNO_4$ (350.2) Calcd. C 51.4 H 3.45 N 4.0 Found C 51.4 H 3.31 N 4.1.- IR: $\tilde{\nu}$max = 3514 (OH), 1712 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 211 (4.20), 241 (4.10), 273 (4.31), 314 (3.85), 352 (sh, 3.70), 455 (3.47); + HCl: 212 (4.19), 240 (4.17), 273 (4.33), 314 (3.95), 360 (3.71), 435 (3.42); + NaOH: 247 (4.06), 291 (4.23), 356 (4.05), 530 nm (2.91).- ^{1}H-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 2.52 (s, 3H, CH_3), 3.97 (s, 3H, 2-OCH_3), 4.03 (s, 3H, 8-OCH_3), 7.14 (s, 1H, 6-H), 8.11 (s, 1H, 3-H).- ^{13}C-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 10.0 (CH_3), 56.9 (2-OCH_3), 62.2 (8-OCH_3), 110.4 (C-5), 126.8 (C-6), 127.4 (C-9a), 128.6 (C-8a), 132.1 (C-4b), 134.2 (C-3), 138.1 (C-1), 147.4 (C-8), 153.6 (C-7), 154.9 (C-2), 157.1 (C-4a), 190.7 (C-9).- MS: m/z (rel.Int. > 20%) = 351 (95, $M_1^{+\cdot}$), 349 (100, $M_2^{+\cdot}$), 333 (33), 331 (30), 306 (23), 305 (22), 252 (40), 224 (57), 85 (30), 83 (44).

5-Bromo-7,8-dihydroxy-2-methoxyonychine

The aqueous $NaHCO_3$-phase from the reaction of **4f** with polyphosphoric acid was adjusted to pH 5 with diluted HCl and extracted with CH_2Cl_2. Work up without further purification gave 5-bromo-7-hydroxy-2,8-dimethoxyonychine.- Yield 32 mg (16%); orange-red crystals.- Mp. > 325°C (MeOH).- TLC: Rf 0.06 ($CHCl_3$-MeOH (9:1)).- $C_{14}H_{10}BrNO_4$ · MeOH (368.2) Calcd. C 48.9 H 3.83 N 3.8 Found C 49.2 H 3.84 N 4.1.- IR (KBr): $\tilde{\nu}$max = 3440, 3380 (OH), 1690 cm^{-1} (CO).- UV/VIS (EtOH): λmax (lg ε) = 210 (4.32), 245 (4.27), 270 (4.36), 310 (3.95), 323 (3.93), 458 (3.32); + HCl: 212 (4.29), 226 (sh, 4.24), 244 (4.26), 272 (4.34), 312 (sh, 3.98), 323 (3.98), 349 (3.88), 370 (sh, 3.82), 441 (3.39); + NaOH: 237 (4.31), 287 (4.24), 311 (sh, 4.02), 364 (4.09), 530 nm (3.60).- ^{1}H-NMR (C_5D_5N): δ (ppm) = 2.55 (s, 3H, CH_3), 3.76 (s, 3H, 2-OCH_3), 7.0 (br s, 1H, 7-OH), 7.45 (s, 1H, 6-H), 8.28 (s, 1H, 3-H), 12.0 (br s, 1H, 8-OH).- ^{13}C-NMR ([D_6]DMSO): δ (ppm) = 9.5 (CH_3), 56.6 (2-OCH_3), 103.5 (C-5), 123.5 (C-6), 121.3, 126.2 and 129.5 (C-9a, C-8a and C-4b), 134.5 (C-3), 135.2 (C-1), 145.8 (C-8), 149.4 (C-7), 153.4 (C-2), 155.3 (C-4a), 190.1 (C-9).- MS: m/z (rel.Int.) = 337 (100, $M_1^{+\cdot}$), 336 (20), 335 (95, $M_2^{+\cdot}$), 322 (19), 320 (24), 294 (60), 292 (55), 213 (27), 185 (19).

7-Hydroxy-2,8-dimethoxyonychine (**1f**)

From 16 mg 5-bromo-7-hydroxy-2,8-dimethoxyonychine by catalytic hydrogenation with Raney nickel in 5 ml EtOAc-MeOH (1:1) under addition of ca. 100 mg NaOAc (room temp., 18 h). Purification by CC on silica gel ($CHCl_3$-acetone (9:1)).- Yield 12 mg (97%); yellow-orange crystals.- Mp. 213-215°C ($CHCl_3$).- TLC: Rf 0.2 ($CHCl_3$-acetone (9:1)).- HR-MS: m/z (rel.Int.) = 271.0847 (calcd. for $C_{15}H_{13}NO_4$: 271.0845) (100, $M^{+\cdot}$).- All physicochemical properties (UV/VIS, IR, ^{1}H-NMR, ^{13}C-NMR, MS) agree with those of an authentic sample isolated from *Piptostigma fugax*[1].- ^{13}C-NMR ($CDCl_3$-CD_3OD): δ (ppm) = 10.0 (CH_3), 56.9 (2-OCH_3), 62.2 (8-OCH_3), 116.6 (C-5), 122.5 (C-6), 126.7 (C-8a), 127.3 (C-9a), 133.6 (C-3), 135.1 (C-4b), 138.7 (C-1), 147.4 (C-8), 152.9 (C-7), 155.2 (C-2), 157.6 (C-4a), 191.6 (C-9).

Thanks are due to the Deutsche Forschungsgemeinschaft and to the Fonds der Chemischen Industrie for financial support.

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