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NEW AZAFLUORENE ALKALOIDS FROM *OXANDRA XYLOPIOIDES*

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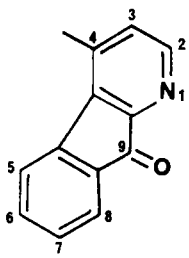
ABSTRACT.—Three new azafluorene alkaloids were isolated from *Oxandra xylopioidies*. The structures of the alkaloids, as determined by organic syntheses and/or spectral analyses, were shown to be 4-azafluorenones, 6-hydroxyonychine [**3**], 5-hydroxy-6-methoxyonychine [**4**], and 2,6-dimethoxy-7-hydroxyonychine [**5**]. The syntheses also provided three additional azaflourenone alkaloids, which were identified as 5,6-dimethoxyonychine [**6**], 8-hydroxyonychine [**7**], and 5,8-dimethoxyonychine [**8**]. The physical and spectral properties of these azafluorene alkaloids are discussed.

In 1976, De Almeida *et al.* (1) isolated the novel alkaloid onychine from *Onychopetalum amazonicum* (Annonaceae). Its structure was assigned as 1-aza-4-methylfluoren-9-one [**1**]. In 1979, Koyama *et al.* (2) synthesized both 1-aza-4-methylfluoren-9-one [**1**] and its structural isomer, 1-methyl-4-azafluoren-9-one [**2**]. Based upon the nmr data of these synthetic products and onychine, they suggested that the structure of onychine be revised to 1-methyl-4-azafluoren-9-one [**2**], although a direct comparison of the synthetic products with onychine was not carried out. Later, reference (3) to and isolation [from *Cleistopholis patens* (Annonaceae)] (4) of onychine still regarded the structure as **1**. This was also the case when 6-methoxyonychine was reported (5) without reference to the revised (2) structure for onychine.

In our laboratory three new alkaloids were isolated from *Oxandra xylopioides* Diels (Annonaceae). Spectral data suggested they were onychine analogues. At this point erroneous structures were published (6,7) for these compounds, based upon the prior references that regarded the structure of onychine as **1**. In view of the uncertainty of the structure of onychine, synthetic methods were employed to produce several 4-azaflouren-9-one derivatives via phenylnicotinic acids (8) in order to establish firmly the structures of the isolates.

The three alkaloids isolated from *O. xylopioides* were shown to be 6-hydroxyonychine [**3**], 5-hydroxy-6-methoxyonychine [**4**], and 2,6-dimethoxy-7-hydroxyonychine [**5**]. The syntheses provided three additional azafluorene alkaloids, 5,6-dimethoxyonychine [**6**], 8-hydroxyonychine [**7**], and 5,8-dimethoxyonychine [**8**].

The uv and ir data of the three natural products indicated they were analogues of onychine (1-methyl-4-azafluoren-9-one) [**2**]. The mass spectra showed molecular ions at *m/z* 211 (16 amu higher than **2**), 241 (46 amu larger than **2**), and 271 (76 amu higher than **2**) suggesting hydroxy-, hydroxy-methoxy-, and dimethoxy-hydroxy-derivatives, respectively.



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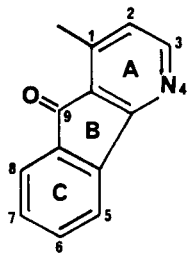

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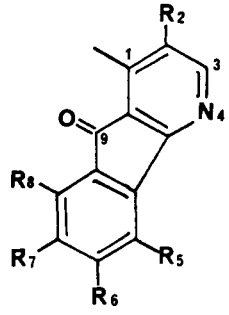

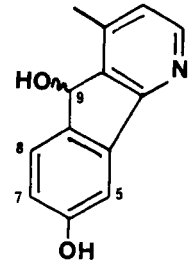

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3 R_6=OH, R_2=R_5=R_7=R_8=H
4 R_5=OH, R_6=OMe, R_2=R_7=R_8=H
5 R_2=R_6=OMe, R_7=OH, R_5=R_8=H
6 R_5=R_6=OMe, R_2=R_7=R_8=H
7 R_8=OH, R_2=R_5=R_6=R_7=H
8 R_5=R_8=OMe, R_2=R_6=R_7=H
9 R_5=OAc, R_6=OMe, R_2=R_6=R_7=H

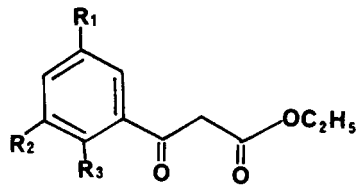
The ^{1}H nmr of 6-hydroxyonychine (M^+ *m/z* 211) [**3**] showed five aromatic signals (ring A—AB system; ring C—AMX system) consistent with the placement of a hydroxy group at C-6 or C-7. The ^{1}H nmr of its dihydro derivative (6-hydroxy-9-dihydroonychine [**10**]) showed a moderate upfield shift and additional splitting ($J_{8,9}$) of H-8 (δ 7.42, dd, $J_{7,8}$=7.2 Hz, $J_{8,9}$=2.6 Hz). In addition, the signal for H-5 shifted downfield to δ 7.67 (d, $J_{5,7}$=2.2 Hz). These facts could be attributed to the molecular tilting, which resulted from the formation of the central cyclopentadienol ring (9). This allowed the assignment of H-8 and H-5 and, thus, showed that the hydroxy substituent was located at C-6. Synthesis confirmed the structure as 6-hydroxyonychine (6-hydroxy-1-methyl-4-azafluoren-9-one) [**3**].

The ^{1}H nmr of 5-hydroxy-6-methoxyonychine (M^+ *m/z* 241) [**4**] showed the presence of one methoxy [δ 4.21 (3H, s)] and four aromatic protons. Two of the aromatic protons were *ortho*-coupled, ring-A protons at δ 6.95 and 8.47 (J=5.7 Hz) (H-2 and H-3, respectively), while the other were *ortho*-coupled and occurred at δ 6.94 and 7.45 (J=7.9 Hz). This indicated that both substituents (hydroxy and methoxy groups) were located on ring C at positions allowing the protons to be *ortho*-distributed. Acetylation of **4** gave an *O*-acetyl derivative (M^+ *m/z* 283) (5-acetoxy-6-methoxyonychine) [**9**], while methylation afforded a dimethoxy derivative (M^+*m/z* 255) (5,6-dimethoxyonychine) [**6**], which had a second methoxy signal at δ 3.97 (3H, s). To confirm the substitution pattern of the natural product, the *O*-methyl derivative was compared to synthetic 5,6-dimethoxyonychine [**6**] and 5,8-dimethoxyonychine [**8**]. The former was identical (ir, ^{1}H nmr, mmp) to the derivative of the natural product. Thus, the isolated alkaloid could be either 5-hydroxy-6-methoxyonychine or 6-hydroxy-5-methoxyonychine. A nOe experiment showed that the methoxy group was adjacent to the aromatic proton at δ 6.94 (9%). Compound **4** showed a sharp peak at 3450 cm^{-1} in the ir spectrum and had a remarkably low melting point (140-142°) compared to the other compounds (6-hydroxyonychine=245-248° and 2,6-dimethoxy-7-hydroxyonychine=271-273°). The ir peak, the low melting point, and a significant loss of H_2O (M^+-H_2O at *m/z* 223; 84%) could be caused by intramolecular hydrogen bonding between the phenolic hydroxy and the nitrogen. Therefore, the natural product is suggested to be 5-hydroxy-6-methoxyonychine (5-hydroxy-6-methoxy-1-methyl-4-azafluoren-9-one) [**4**].

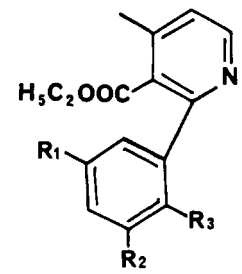
The ^{1}H nmr of 2,6-dimethoxy-7-hydroxyonychine (M^+ *m/z* 271) [**5**] showed the presence of 2 methoxy signals at δ 3.94 (6H, s) and three one proton aromatic singlets

at δ 7.15, 7.18, and 7.83. Thus, one of the three substituents (2 methoxys and 1 hydroxy) were attached to ring A and two on ring C in such a fashion as not to allow an *ortho*- or *meta*-relationship among any of the protons, i.e., 2,6,7-trisubstitution or 3,6,7-trisubstitution. Because H-3 is the most downfield proton and the chemical shift of H-2 in this group of alkaloids did not exceed δ 7.2, the signal at 7.83 should represent H-3. The presence of either a methoxy or hydroxy group at C-2 would shield the proton on the *ortho*-position (H-3). Thus, H-3 occurred relatively upfield (δ 7.83) compared to the other alkaloids in this group. Irradiation of the two methoxy signals at δ 3.94 showed an enhancement of the protons at δ 7.18 (12%) and 7.83 (14%). Therefore, one methoxy group should be located at C-2 and the other substituents (hydroxy and methoxy) at C-6 and C-7. The uv spectrum of this compound in basic solution revealed a remarkable color change and absorption around 485 nm. Obviously, this involved the disassociation of the phenolic proton and the formation of an enolate with an extended conjugated system. Positioning of the hydroxy at C-7 allowed for a greater delocalization than if it were placed at C-6. Therefore, it is proposed that this natural product should be 2,6-dimethoxy-7-hydroxyonychine (2,6-dimethoxy-7-hydroxy-1-methyl-4-azafluoren-9-one [**5**].

8-Hydroxyonychine [**7**] was formed during the synthesis of 6-hydroxyonychine [**3**]. The ms (M^+ *m/z* 211) of 8-hydroxyonychine [**7**] indicated that this by-product of the final step of the synthetic scheme was an isomer of 6-hydroxyonychine [**3**]. 8-Hydroxyonychine [**7**] showed signals for five aromatic protons (ring A—AB system; ring B—ABC system) consistent with the placement of the hydroxy group at C-8. Its low melting point (mp 140-142°) compared to 6-hydroxyonychine (mp 245-248°) further indicated the location of the hydroxy at C-8, which would allow for the formation of an intramolecular hydrogen bond between the hydroxy and the carbonyl at C-9. Thus, this compound is shown to be 8-hydroxyonychine (8-hydroxy-1-methyl-4-azafluoren-9-one) [**7**].



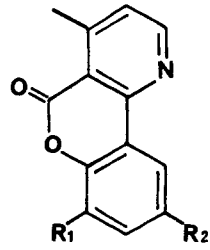
11a R_2=OH, R_1=R_3=H
11b R_1=R_3=OMe, R_2=H
11c R_2=R_3=OMe, R_1=H



12a R_2=OH, R_1=R_3=H
12b R_1=R_3=OMe, R_2=H
12c R_2=R_3=OMe, R_1=H

Therefore, six onychine alkaloids have been brought to light by the isolation and syntheses. In addition, by-products of the synthetic scheme, two phenylnicotinic-δ-lactones [**13** and **14**], were produced.

The direct comparison of the synthetic products with two of the naturally occurring azafluorene alkaloids has further confirmed the structure of onychine as revised by Koyama *et al.* (2). As a unique group of alkaloids, azafluorenes showed characteristic uv, nmr, and mass spectra. Generally, the substituted onychines (1-methyl-4-azafluorenones) gave three absorption bands in their uv spectra (MeOH); Bands I (245-250 nm), II (280-300 nm), and III (340-350 nm or above). Upon addition of acid, the intensity of Band I dramatically decreased, while Bands II and III showed red shifts. In the case of phenolic derivatives, addition of base would cause a moderate red shift of



13 R_2=OMe, R_1=H
14 R_1=OMe, R_2=H

Band II and an enormous shift (435-486 nm) of Band III depending on the phenolic position. The major mass fragmentations of these alkaloids are due to the structural skeleton, which involves loss of the carbonyl, part of ring A, and the loss of the substituent groups. In the case of phenolic onychinoids, the loss of carbon monoxide from ring C also occurred. There were variations of the fragmentation pattern for the 5-methoxyonychinoids. These derivatives gave a strong M^+-1 peak followed by the loss of a carbonyl group. This may be explained by the formation of a 6-membered ring between the 5-methoxy and the nitrogen.

EXPERIMENTAL

PLANT MATERIAL.—The stem bark (1.5 kg) and twigs (1.06 kg) of *O. xylopioides* were collected in May 1979, in Peru. Herbarium specimens are deposited at the Natural Arboretum, USDA (No. PR 51790 and 51791).

GENERAL EXPERIMENTAL PROCEDURES.—Column chromatography was carried out on 100 mesh silicic acid (Mallinckrodt) or 70-230 mesh Kieselgel 60 (E. Merck); tlc with 5×20 cm commercial Si gel on aluminum plates (E. Merck) visualized with modified Dragendorff's Reagent (10); centrifugal chromatography with a Chromatotron Model 7924 equipped with a FIMLAB Pump Model RP-G150. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv and visible spectra were determined on a Perkin-Elmer Model 552A uv/vis spectrophotometer. Ir spectra were obtained on a Perkin-Elmer Model 267 grating infrared spectrophotometer. Nmr spectra were obtained from either a 60 MHz Hitachi Perkin-Elmer Model R-24 spectrometer or a JEOL FX-90Q, 90 MHz spectrometer in either $CDCl_3$ or CD_3OD solution. The nOe experiments were done by direct measurements. A Finnigan 3200 GC/MS System with dedicated data system was used to obtain mass spectral data. High resolution mass spectra were taken on a Varian Mat, model CH5 mass spectrometer.

EXTRACTION AND FRACTIONATION.—The plant material was exhaustively extracted by percolation with EtOH. Extracts of the stem bark (272 g) and twigs (262 g) showed identical composition by tlc and were combined and submitted to a standard acid-base partition scheme. The resulting nonquaternary alkaloid fraction (27.2 g) was separated into a phenolic alkaloid fraction (3.4 g) and a non-phenolic alkaloid fraction (22.7 g) via partitioning with 5% NaOH.

ISOLATION OF ALKALOIDS.—The phenolic alkaloidal fraction (3.4 g) was dissolved in $CHCl_3$-MeOH (1:1), adsorbed onto silicic acid (3 g) and chromatographed over a silicic acid column (180 g; 4×41 cm) packed in $CHCl_3$. Elution was started with $CHCl_3$ and the polarity gradually increased with MeOH. Fractions of 500 ml were collected.

5-HYDROXY-6-METHOXYONYCHINE [**4**].—Elution with $CHCl_3$ afforded a yellow residue (71 mg), which crystallized from petroleum ether as yellowish prisms of **4**; mp 140-142°; uv λ max (MeOH) 243 sh nm (log ε 4.06), 250 (4.11), 280 sh (3.77), 289 (3.79), 300 (3.73), 355 (2.73); (MeOH+NaOH): 252 (4.06), 300 (3.66), 320 (3.69), 450 (3.28); (MeOH+HCl) 243 (3.86), 250 sh (3.83), 317 (3.88); ir ν max (KBr) 3450, 1710, 1600, 1565, 1490, 1440, 1380, 1320, 1275, 1255, 1235, 1200, 1115, 1075, 1010, 940, 880, 815, 800, 740, 720 cm^{-1}; ^1H nmr (90 MHz) ($CDCl_3$) δ 2.63 (3H, s) (C-1-Me), 4.21 (3H, s, C-6-OMe), 6.94 (1H, d, $J_{7,8}$=7.9 Hz) (H-7), 6.95 (1H, d, $J_{2,3}$=5.7 Hz) (H-2), 7.45 (1H, d, basified with conc. NH_4OH to pH 8 and extracted with $CHCl_3$ (5×10 ml). The $CHCl_3$ extracts were combined, dried (Na_2SO_4), filtered, and evaporated to an amorphous residue (7 mg); ir ν max (KBr) 2930, 2860, 1765, 1710, 1595, 1470, 1430, 1375, 1280, 1270, 1250, 1208, 1160, 1075, 1020, 960, 940, 900, 875, 840, 810, 725 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 2.38 (3H, s) (C-5-OAc), 2.64 (3H, s) (C-1-

Me), 4.08 (3H, s) (C-6-OMe), 6.95 (1H, d, $J_{2,3}$=5.8 Hz) (H-2), 7.05 (1H, d, $J_{7,8}$=7.5 Hz) (H-7), 7.48 (1H, d, $J_{7,8}$=7.5 Hz) (H-8), 8.48 (1H, d, $J_{2,3}$=5.8 Hz) (H-3); ms *m/z* 283 (40%, M^+); 241 (100), 223 (98), 212 (67), 195 (37), 183 (50).

6-HYDROXY-9-DIHYDROONYCHINE [**10**].—6-Hydroxyonychine [**3**] (2.5 mg) was dissolved in absolute EtOH (2 ml) and hydrogenated over 10% Pd/C (5 mg) at atmospheric pressure for 3 h. The solution was filtered and the Pd/C residue washed with EtOH (2 ml×3). The filtrate was evaporated to afford a yellow-white residue (1.5 mg); uv λ max (MeOH) 280 sh nm (log ε 3.98), 289 (3.86), 315 (3.75); (MeOH+NaOH) 243 sh (4.14), 289 (3.92), 300 (3.84), 350 (3.50); (MeOH+HCl) 220 sh (4.41), 308 (3.78), 350 (3.65); ir ν max (KBr) 3420 br, 2930, 2860, 1610, 1510, 1465, 1385 cm^{-1}; ^1H nmr (90 MHz) (CD_3OD) δ 2.47 (3H, s) (C-1-Me), 3.62 (1H, d, $J_{8,9}$=2.6 Hz) (H-9), 6.89 (1H, dd, $J_{5,7}$=2.2, $J_{7,8}$=7.2 Hz) (H-7), 7.16 (1H, d, $J_{2,3}$=5.2 Hz) (H-2), 7.42 (1H, dd, $J_{8,9}$=2.6, $J_{7,8}$=7.2 Hz) (H-8), 7.67 (1H, d, $J_{5,7}$=2.2 Hz) (H-5), 8.35 (1H, d, $J_{2,3}$=5.2 Hz) (H-3).

SYNTHESIS OF 6-HYDROXYONYCHINE [**3**] AND 8-HYDROXYONYCHINE [**7**].—*Ethyl 4-Methyl-2-(3-hydroxyphenyl)nicontinate* [**12a**].—The ester **11a** (11) (5.0 g) was dissolved in EtOH (50 ml) and stirred on an ice-bath; conc. NH_4OH (6 ml) was added, followed by crotonaldehyde (8 ml) at such a rate that the temperature of the solution remained below 10°. The mixture was kept overnight at room temperature, then the residue was placed on a silicic acid column. Elution with Me_2CO-EtOAc (2:1) afforded ethyl 4-methyl-2-(3-hydroxyphenyl)nicotinate (450 mg) (7.2% yield) as a yellow amorphous residue; uv λ max (MeOH) 250 nm (log ε 3.56), 280 (3.33); (MeOH+NaOH) 230 (3.90); (MeOH+HCl) 268 (3.44); ir ν max (KBr) 3100-3500, 3000, 1725, 1580, 1440, 1240, 1130, 1060, 700 cm^{-1}; ^1H nmr (90 MHz) ($CDCl_3$) δ 1.03 (3H, t, J=7.0), 2.42 (3H, s), 4.14 (2H, q, J=7.0), 6.70-7.20 (4H, m), 7.16 (1H, d, J=5.3), 8.50 (1H, d, J=5.3); ms *m/z* 258 (16%, M^++1), 229 (14), 228 (100), 212 (76), 185 (18), 183 (10), 158 (10), 154 (18), 128 (11), 91 (16).

4-Methyl-2-(3-hydroxyphenyl)nicotinic Acid.—A solution of nicotinate [**12a**] (450 mg) in aqueous KOH (40%, 10 ml) was refluxed overnight. The mixture was acidified with HCl, basified with conc. NH_4OH (pH 10), and extracted with $CHCl_3$ to remove any unreacted starting material. After the H_2O was removed under vacuum, the mixture was extracted several times with hot MeOH. The MeOH solutions were combined and concentrated to a residue which was purified on a silicic acid column eluted with MeOH. 4-Methyl-2-(3-hydroxylphenyl)nicotinic acid (300 mg) crystallized from H_2O as white needles; mp 260-262°; uv λ max (MeOH) 246 nm (log ε 3.48), 275 (3.70); (MeOH+NaOH) 243 (3.84), 278 (3.75); (MeOH+HCl) 273 (3.78); ir ν max (KBr) 2500-3500, 1625, 1585, 1365, 820, 700 cm^{-1}; ^1H nmr (90 MHz) (CD_3OD) δ 2.47 (3H, s), 6.86 (1H, ddd, J=7.0, 2.2, 2.2 Hz), 7.1-7.4 (4H, m), 8.40 (1H); ms *m/z* 229 (90%, M^+), 215 (9), 213 (42), 201 (12), 185 (100), 170 (15), 157 (52), 154 (22), 131 (16), 127 (20), 114 (15), 92 (31), 77 (70).

Formation of 6-Hydroxyonychine [**3**] *and 8-Hydroxyonychine* [**7**].—4-Methyl-2-(3-hydroxyphenyl)nicotinic acid (100 mg) was stirred with polyphosphoric acid (30 ml) at 130° for 3 h. After cooling, ice H_2O (100 ml) followed by conc. NH_4OH (pH 10) was added. The solution was extracted several times with $CHCl_3$. The $CHCl_3$ layers were combined and concentrated to yield a yellow residue (24 mg). The residue showed two spots on tlc ($CDCl_3$-Me_2CO, 3:1). Chromatography over a Si gel column (0.4 cm×8 cm) with $CHCl_3$ afforded two products, **3** (6.7 mg) and **7** (5.6 mg). 6-Hydroxyonychine [**3**]: yellow needles; mp 243-245°; identical [uv, ir, ^1H nmr, mmp (242-245°)] to the natural product. 8-Hydroxyonychine [**7**]: yellow needles ($CHCl_3$); mp 140-142°; uv λ max (MeOH) 226 nm (log ε 4.43), 247 (4.69), 288 (4.72), 300 (4.14), 362 (3.34); (MeOH+NaOH) 240 (4.63), 293 (4.22), 302 (4.20), 435 (3.91); (MeOH+HCl) 226 (4.38), 248 (4.63), 290 (4.23), 302 (4.30), 373 (3.78); ir ν max (KBr) 3400, 1700, 1600, 1580, 1570, 1240, 1120, 1035, 920, 800 cm^{-1}; ^1H nmr (90 MHz) ($CDCl_3$) δ 2.62 (3H, s) (C-1-Me), 6.88 (1H, dd, $J_{6,7}$=7.5, $J_{5,7}$=1.3 Hz) (H-7), 6.96 (1H, d, $J_{2,3}$=5.7 Hz) (H-2), 7.33 (1H, dd, $J_{5,6}$=7.5, $J_{5,7}$=1.3 Hz) (H-5), 7.47 (1H, dd, $J_{5,6}$=7.5, $J_{6,7}$=7.5 Hz) (H-6), 8.42 (1H, d, $J_{2,3}$=5.7 Hz) (H-3), 11.80 (1H, s) (C-8-OH); ms *m/z* 211 (100%, M^+), 183 (31), 164 (14), 154 (28), 126 (12), 92 (14).

SYNTHESIS OF 5,8-DIMETHOXYONYCHINE [**8**].—*Ethyl 4-Methyl-2(2,5-dimethoxyphenyl)nicotinate* [**12b**].—Compound **12b** was prepared as described above for **12a** starting with ethyl 2,5-dimethoxyphenylacetoacetate [**11b**] (11) (4.5 g). Chromatography of the reaction mixture (2.2 g) on a silicic acid column (4 cm×40 cm) eluted with EtOAc-petroleum ether (8:2) afforded ethyl 4-methyl-2-(2,5-dimethoxylphenyl)nicotinate (100 mg) (1.9% yield) as a yellow residue; uv λ max (MeOH) 303 nm (log ε 3.55); (MeOH+HCl) 265 (3.78), 335 (3.30); ir ν max (KBr) 1730, 1580, 1500, 1460, 1430, 1270, 1220, 1180, 1125, 1065, 1045, 1020, 805, 720 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 0.97 (3H, t, J=7 Hz), 2.46 (3H, s), 3.68 (3H, s), 3.77 (3H, s), 4.05 (2H, q, J=7 Hz), 6.8-7.0 (3H, m), 7.12 (1H, d, J=5 Hz), 8.55 (1H, d, J=5 Hz).

4-Methyl-2-(2,5-dimethoxyphenyl)nicotinic Acid.—The nicotinate acid was prepared as described above for 4-methyl-2-(3-hydroxyphenyl)nicotinic acid starting with **12b** (100 mg). Crystallization from H_2O gave the nicotinic acid (75 mg) (82.7% yield) as white needles; mp 178-180°; uv λ max (MeOH) 263 nm (log ε 3.15), 300 (3.18); (MeOH+HCl) 267 (3.42), 337 (2.97); ir ν max (KBr) 3500-3100, 1610, 1590, 1500, 1220, 1030, 820 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 2.38 (3H, s), 3.56 (3H, s), 3.72 (3H, s), 6.70-7.20 (4H, m), 8.5 (1H); ms *m/z* 273 (93%, M^+), 258 (9), 243 (9), 229 (100), 214 (10), 198 (12), 185 (5), 170 (8).

5,8-Dimethoxyonychine [**8**] *and 4-Methyl-2-(2-oxy-5-methoxyphenyl)nicotinic-δ-lactone* [**13**].—The nicotinic acid (100 mg) and polyphosphorus acid (30 ml) were heated and stirred at 130° for 3 h. After cooling, the mixture was diluted with ice H_2O, basified with NH_4OH, and then extracted several times with $CHCl_3$. The extracts were combined and concentrated to dryness. Separation on Si gel preparative tlc afforded two products, a major product (80 mg) and a minor product (6 mg), the latter was determined to be the desired product. 5,8-Dimethoxyonychine [**8**] (minor product-6.4%): mp 140-145°; uv λ max (MeOH) 228 nm (log ε 4.23), 248 (4.23), 299 (3.58), 312 (3.55), 420 (3.16); (MeOH+HCl) 250 (3.97), 297 (3.77), 325 (3.50), 430 (3.34); ir ν max (KBr) 1700, 1600, 1500, 1470, 1270, 1040, 810 cm^{-1}; ^1H nmr (90 MHz) ($CHCl_3$) δ 2.62 (3H, s) (C-1-Me), 3.96 (3H, s) (C-5-OMe), 4.02 (3H, s) (C-8-OMe), 6.90 (1H, d, $J_{2,3}$=5.3 Hz) (H-2), 6.93 (1H, d, $J_{6,7}$=9.2 Hz) (H-7), 7.61 (1H, d, $J_{6,7}$=9.2 Hz) (H-6), 8.50 (1H, d, $J_{2,3}$=5.3 Hz) (H-3); ms *m/z* 255 (66%, M^+), 254 (100), 240 (63), 266 (48). 4-Methyl-2-(2-oxymethyoxyphenyl)nicotinic-δ-lactone [**13**] (major product-80%): white needles mp 63-65° ($CHCl_3$); uv λ max ($CHCl_3$) 265 nm (log ε 3.93), 319 (3.61); ir ν max (KBr) 1730, 1585, 1500, 1470, 1245, 1050, 1035, 820 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 2.70 (3H, s), 3.83 (3H, s), 7.00-7.30 (3H, m), 7.95 (1H, d, J=3 Hz), 8.70 (1H, d, J=6 Hz); ms *m/z* 241 (100%, M^+), 226 (15), 198 (22), 170 (25).

SYNTHESIS OF 5,6-DIMETHOXYONYCHINE [**6**].—*Ethyl 4-Methyl-2-(2,3-dimethoxyphenyl)nicotinate* [**12c**].—Compound **12c** was prepared as described above for **12a** starting with ester **11c** (11) (7 g). Column chromatography of the reaction mixture (5.7 g) on silicic acid (Me_2CO-EtOAc, 8:2) afforded **12c** (175 mg, 2.1%) as a yellow residue; uv λ max (MeOH) 223 nm (log ε 4.28), 250 (3.91), 273 (3.89); ir ν max (KBr) 1720, 1575, 1470, 1260, 1120, 1005, 750 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 1.00 (3-H, t, J=7 Hz), 2.47 (3H, s), 3.64 (3H, s), 3.89 (3H, s), 4.08 (2H, q, J=7 Hz), 6.8-7.3 (4H, m), 8.55 (1H, d, J=5 Hz); ms *m/z* 302 (3%, M^++1), 301 (19, M^+), 229 (15), 228 (100), 226 (20), 198 (11), 166 (12), 165 (79), 122 (10).

4-Methyl-2-(2,3-dimethoxyphenyl)nicotinic acid.—The nicotinic acid was prepared as described above for 4-methyl-2-(3-hydroxyphenyl)nicotinic acid starting with **12c** (175 mg). Crystallization from H_2O afforded the nicotinic acid (100 mg) (63%) as white needles; mp 180-182°; uv λ max (MeOH) 268 nm (log ε 3.31), 330 (2.50); ir ν max (KBr) 3600-3100, 1670, 1600, 1580, 1445, 1400, 1305, 1280, 1240, 1220, 990, 820, 780 cm^{-1}; ^1H nmr (60 MHz) (CD_3OD) δ 2.50 (3H, s), 3.63 (3H, s), 3.86 (3H, s), 6.9-7.5 (4H, m), 8.4 (1H, br); ms *m/z* 272 (1%, M^++1), 243 (11), 241 (100), 226 (12), 198 (24), 170 (52), 157 (56), 115 (40).

5,6-Dimethoxyonychine [**6**] *and 4-Methyl-2-(2-oxy-3-methoxyphenyl)nicotinic-δ-lactone* [**14**].—The nicotinic acid (100 mg) was stirred with polyphosphorus acid (30 ml) at 130° for 1 h. The mixture was diluted with ice H_2O (20 ml) and basified with conc. NH_4OH (pH 10). The solution was extracted several times with $CHCl_3$. The extracts were combined and dried (Na_2SO_4). Separation on a small Si gel column (0.4 cm×4 cm, $CHCl_3$) gave a major (75 mg) and minor product (7.5 mg), the latter being the target alkaloid. 5,6-Dimethoxyonychine [**6**] (minor product-7.7%): yellow needles (MeOH) mp 149-150°; identical [uv, ir, ^1H nmr, mmp (148-149°)] to the methylated derivative of the natural product. 4-Methyl-2-(2-oxy-3-methoxyphenyl)nicotinic-δ-lactone [**14**] (major product-75%): white needles ($CHCl_3$): mp 58-60°; uv λ max ($CHCl_3$) 267 nm (log ε 3.96), 325 (3.66); ir ν max (KBr) 1715, 1575, 1480, 1250, 1200, 1050, 800 cm^{-1}; ^1H nmr (60 MHz) ($CDCl_3$) δ 2.86 (3H, s), 3.98 (3H, s), 7.00-7.40 (3H, m), 8.13 (1H, dd, J=7.3 Hz), 8.77 (1H, d, J=6 Hz); ms *m/z* 241 (100%, M^+), 226 (9), 198 (130), 170 (18).

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