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SYNTHESIS OF AZANAPHTHOQUINONE ANNELATED PYRROLES

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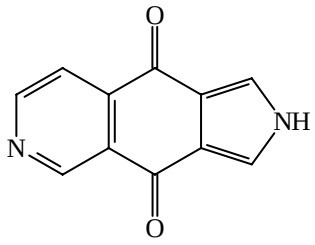
Abstract - The synthesis of azanaphthoquinone annelated pyrrole derivatives is described. The [*c*]-annelated derivative was synthesized by reaction of an azanaphthoquinone monoketal with tosylmethyl isocyanide. The synthesis of each of the two isomeric [*b*]-annelated pyrrole derivatives was realized by selective acylation reactions with pyrrole. Furthermore detailed NMR spectroscopic studies (^{1}H, ^{13}C) are published.

INTRODUCTION

In continuation of our studies[1] concerning the synthesis of pharmacologically active pyrrole and isoindole derivatives we were interested in compounds (**1**), (**2**) and (**3**), which should serve as starting materials in the projected syntheses of potentially cytostatic agents. Since quinones were unsuitable starting materials in the reaction with tosylmethyl isocyanide for the synthesis of isoindoles, we envisaged the reaction with an appropriate monoketal for the preparation of the [*c*]-annelated pyrrole (**1**).[1]



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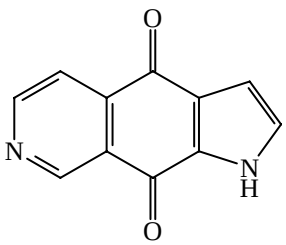

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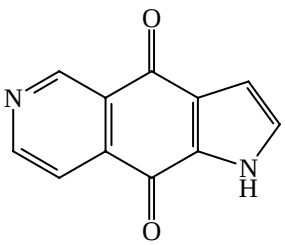

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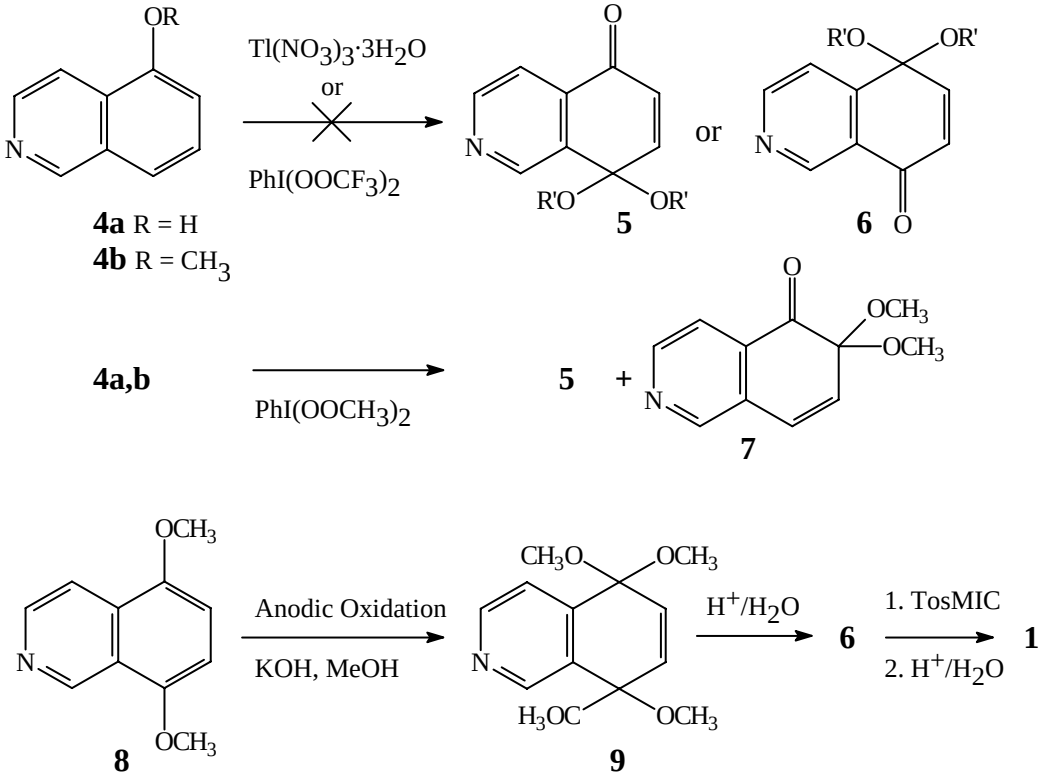
An efficient synthesis of the new azanaphthoquinone monoketal (**5/6**) had to be worked out. The synthesis to the [*b*]-annelated pyrroles (**2**) and (**3**) should be realized by two regioselectively controlled

sequential acylation reactions. Moreover, for all isomeric pyrrole derivatives unambiguous assignements of signals in the ^{1}H and ^{13}C-NMR spectra are presented.

RESULTS AND DISCUSSION

a) Synthesis of [*c*]-annelated azanaphthoquinone pyrrole (**1**):

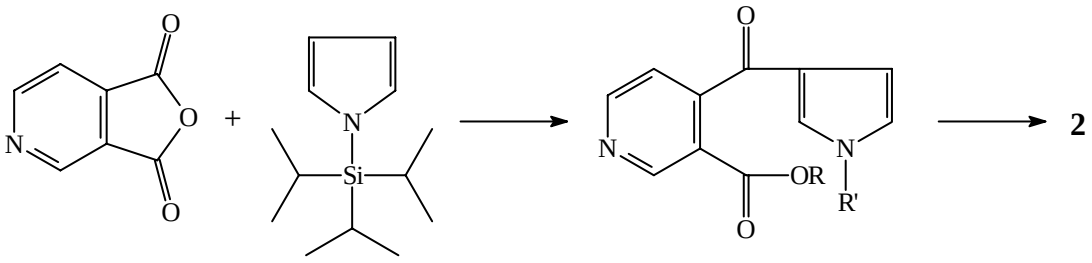
The reaction of α,β-unsaturated carbonyl compounds with tosylmethyl isocyanide represents a suitable way for the straightforward synthesis of 3,4-substituted pyrroles.[1-3] To make use of this reaction type we were in need of monoketal (**5**) or (**6**). Unfortunately established oxidation methods of 5-isoquinolinol (or its methyl ether) with Tl(III) nitrate[4] or iodobenzene bis(trifluoroacetate)[5] were unsuccessful. The reaction of **4a** and **b**, respectively, with iodobenzene diacetate afforded the dimethyl monoketal (**5**) only with poor yields. Moreover the synthesis of **5** was accomanied by the formation of isomer (**7**).



Another way to quinone monoketals can be realized by careful hydrolysis of an appropriate diketal. Indeed diketal (**9**) could be made accessible in high yields by anodic oxidation[6] of 5,8-dimethoxy-isoquinoline (**8**)[7]. Subsequent selective hydrolization[8] afforded nearly quantitatively dimethyl monoketal (**6**). As previously described the reaction sequence with tosylmethyl isocyanide followed by hydrolysis of the ketal finally led to the [*c*]-annelated azanaphthoquinone pyrrole (**1**).

b) Synthesis of [*b*]annelated azanaphthoquinone pyrroles (**2**) and (**3**):

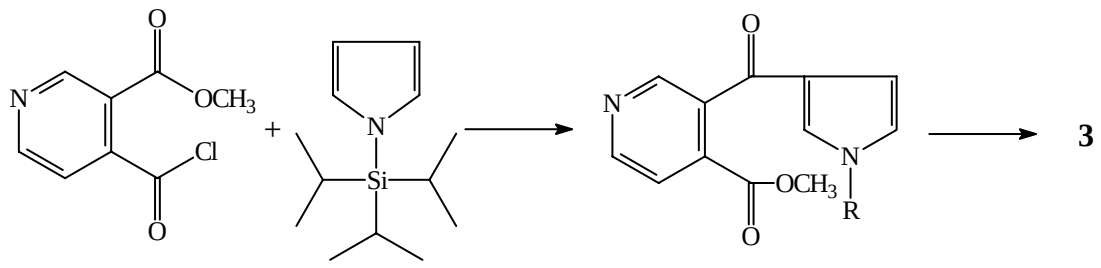
Of critical importance in the synthesis of **2** and **3** was the regioselectivity of the acylation reaction of the pyrrole nucleus. Snieckus' tandem directed metalation reaction[9] could not be exploited for the synthesis of the title compounds because neither 2- nor 3-formylpyrrole (protected as benzyl derivatives)[10,11] gave any reaction with isonicotinic acid amide to furnish **2** or **3**. Other methods to achieve regioselectivity make use of 2-carboxylate substituted pyrroles.[12] But these established methods have the disadvantage of increasing the reaction steps. A convenient approach to realize regioselectivity of the acylation of pyrrole seemed to attach a voluminous *N*-protecting group which allows acylation of pyrrole selectively in the C_3-position. After cleavage of this bulky protecting group subsequently selective intramolecular acylation reaction at C_2-position should finish the synthesis of the title compounds **2** and **3**. For the synthesis of **2** as starting materials pyridine-3,4-dicarboxylic acid anhydride (**10**) and *N*-triisopropylsilyl protected pyrrole derivative (**11**)[13] were selected.



10 **11**

12 R = H, R' = Si(*i*-$C_3H_7)_3$
13 R = CH_3, R' = Si(*i*-$C_3H_7)_3$
14 R = CH_3, R' = H
15 R = CH_3, R' = O_2SPh

Indeed as a consequence of the bulky triisopropylsilyl protecting group acylation with **10** occurs as expected selectively in the C_3-position of the pyrrole nucleus, thus furnishing adduct (**12**) free of isomers. After preparation of the corresponding methyl ester (**13**) with CH_2N_2 and deprotection with tetrabutyl ammonium fluoride[14] (TBAF; furnishing **14**) the treatment with benzenesulfonyl chloride[15] afforded *N*-phenyl sulfonate (**15**). Whereas reaction with lithium diisopropyl amide (LDA) failed, the cyclization with 2 equivalents of lithium hexamethyldisilazide (LiHMDS)[16] was successful. The careful hydrolysis[17] of the *N*-phenyl sulfonate with K_2CO_3 finally led to the title compound (**2**). An obvious straightforward route using phenyl sulfonated pyrrole for the reaction with anhydride (**10**) was unsuccessful and furnished only an inseparable mixture of acylated pyrrole derivatives. Moreover it should be emphasized that this methodology has the great advantage that it could be exploited with a slight modification also for the synthesis of isomer (**3**). Instead of anhydride (**10**) we used acid chloride (**16**)[16] thus obtaining a shift of reactivity from the C_4-carboxylate (in **10**) to the C_3-positioned carboxylic acid chloride (in **16**). As expected the reaction of **16** with **11** furnished C-3 acylated pyrrole (**17**), which was converted to the title compound (**3**) in analogy as described above.



16 **11** **17** R = Si(*i*-C_3H_7)$_3$
18 R = H
19 R = O_2SPh

EXPERIMENTAL

Melting points were detected on a Reichert-Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer. MS spectra were obtained on a Hewlett Packard 5890A/5970B-MSD instrument or on a Shimadzu QP 1000 spectrometer. All NMR spectra were recorded on a Varian Unity*plus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28^{o}C. The solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H, $CDCl_3$), δ 2.49 ppm (^{1}H, DMSO-d_6), δ 77.0 ppm(^{13}C, $CDCl_3$), δ 39.5 ppm (^{13}C, DMSO-d_6),). The digital resolutions were 0.25 Hz/data point for the ^{1}H-NMR spectra and 0.56 Hz/data point for the broad-band decoupled ^{13}C-NMR spectra. Spectral and structural assignments for all compounds investigated were achieved by combined application of standard NMR techniques as described in ref.[1] Anodic oxidations were carried aout with a Elektro-Automatic Laboratory Power Supply (Typ 2326, Viersen, Germany). For column chromatographic separations Merck silica gel 60, 70 - 230 mesh ASTM (Nr. 1.07734) or Aluminia B aluminium oxide (ICN Biomedicals, Nr. 2072) activity grade III were used. Thin layer chromatography was performed on silica gel 60 F_{254} plates (Merck-Nr. 1.05554: 0.2 mm; Merck-Nr. 1.07734: 2.0 mm, 20 x 20 cm) or aluminium oxide 60 F_{254} plates (Merck-Nr. 1.05550: 0.2 mm).

8,8-Dimethoxy-5,8-dihydro-5-isoquinolinone (**5**) and 6,6-Dimethoxy-5,6-dihydro-5-isoquinolinone (**7**)

To a solution of 0.5 g (3.7 mmol) of 5-hydroxyisoquinoline in 14 mL of dry MeOH at 0^{o}C was added 1.5 g (4.6 mmol) of iodobenzene diacetate under Ar atmosphere. After stirring for 1 h at rt the mixture was diluted with ethyl acetate and extracted with saturated aqueous $NaHCO_3$ solution. The formed precipitate was filtered off by suction. The filtrate was dried with anhydrous $MgSO_4$ and carefully concentrated at 30^{o}C. The residue was submitted to preparative TLC (silica gel, 2 mm, eluent: ethyl acetate/light petroleum 1/1, 1% NEt_3) affording a mixture of **5** and **7** (R_f = 0.42). Resolution of **5** and **7** was achieved by TLC (silica gel, 0.2 mm, eluent: pentane/acetone 9/1, 1% NEt_3, 6 developments) affording 26 mg (4.6%) of **5** as semicrystallinic mass and 5 mg (1 %) of **7** as colorless oil. Compound (**5**): IR (KBr): cm^{-1}

2939, 2836, 1683; MS: *m/z* (%) 205 (M^++1, 2), 175 (16), 174 (100), 146 (23), 131 (10), 77 (15), 76 (19), 50 (30); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.29 (s, 6H, OMe), 6.61 (d, *J* = 10.6 Hz, 1H, H-6), 7.05 (d, *J* = 10.6 Hz, H-7), 7.83 (dd, *J* = 5.1 Hz and 0.9 Hz, 1H, H-4), 8.82 (d, *J* = 5.1 Hz, 1H, H-3), 8.82 (d, *J* = 0.9 Hz, 1H, H-1); ^{13}C-NMR ($CDCl_3$): δ (ppm) 51.2 (OMe), 94.1 (C-8), 118.3 (C-4, ^1J = 167.8 Hz), 131.6 (C-6, ^1J = 167.1 Hz), 133.1 (C-8a), 136.4 (C-4a), 144.4 (C-7, ^1J = 163.0 Hz), 149.8 (C-1, ^1J = 183.0 Hz), 150.9 (C-3, ^1J = 183.1 Hz), 183.0 (C-5). HRMS: Calcd for $C_9H_{11}NO_3$: 205.07389. Found: 205.074±0.001. Compound (**7**): IR (NaCl, liquid film): cm^{-1} 2925, 2863, 1708; MS: m/z (%) 205 (M^++1, 56), 177 (80), 175 (29), 174 (100), 146 (56), 132 (38), 118 (21), 76 (25); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.42 (s, 6H, OMe), 6.37 (d, *J* = 10.3 Hz, 1H, H-7), 6.77 (d, *J* = 10.3 Hz, H-8), 7.73 (dd, *J* = 4.9 Hz and 0.7 Hz, 1H, H-4), 8.59 (d, *J* = 0.7 Hz, 1H, H-1), 8.70 (d, *J* = 4.9 Hz, 1H, H-3); ^{13}C-NMR ($CDCl_3$): δ (ppm) 50.5 (OMe), 92.9 (C-6), 119.4 (C-4), 126.8 (C-8), 129.3 (C-8a), 131.5 (C-7), 134.5 (C-4a), 148.9 (C-1), 150.8 (C-3), 193.0 (C-5). HRMS: Calcd for $C_9H_{11}NO_3$: 205.07389. Found: 205.074±0.001.

5,5,8,8-Tetramethoxy-5,8-dihydroisoquinolinone (**9**)

A solution of 5.0 g (26.5 mmol) of 5,8-dimethoxyisoquinoline (**8**)[7] in 150 mL of 1 N methanolic potassium hydroxide was electrolyzed for 2 h (monitored by TLC, silica gel, ethyl acetate/light petroleum 7/3) at rt in an undivided electrolysis cell with Pt-electrodes with a constant potential of 30 V. Afterwards the solvent was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The organic solution was washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* furnishing 5.56 g (84%) of **9**. The crude product can be used for the next reaction step without further purification. For spectroscopic purposes a small quantity of samples was purified by TLC (silica gel, ethyl acetate/light petroleum 7/3, 1% NEt_3) affording a yellowish oil. IR (NaCl, liquid film): cm^{-1} 2942, 2832, 1733, 1597; MS: *m/z* (%) 220 (100), 189 (49), 174 (41), 146 (22), 131 (9), 117 (5), 103 (8), 76 (7); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.20 (s, 6H, C5-OMe), 3.23 (s, 6H, C8-OMe), 6.36 (A-part of an AB-system, *J* = 10.9 Hz, 1H, H-6), 6.40 (B-part of an AB-system, *J* = 10.9 Hz, 1H, H-7), 7.53 (dd, *J* = 5.2 Hz and 0.8 Hz, 1H, H-4), 8.66 (d, *J* = 5.2 Hz, 1H, H-3), 8.91 (d, *J* = 0.8 Hz, 1H, H-1); ^{13}C-NMR ($CDCl_3$): δ (ppm) 50.9 (C8-OMe, ^1J = 142.9 Hz), 51.0 (C5-OMe, ^1J = 143.1 Hz), 94.1 (C-5), 94.5 (C-8), 120.1 (C-4), 131.2 (C-6, ^1J = 163.2 Hz, ^2J = 1.6 Hz), 131.3 (C-8a), 132.1 (C-7, ^1J = 163.2 Hz, ^2J = 1.6 Hz), 144.3 (C-4a), 149.1 (C-1), 149.7 (C-3). HRMS: Calcd for $C_{12}H_{14}NO_3$ (M^+-OCH_3): 220.0974. Found: 220.0974±0.001. *Anal.* Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.87; H, 6.67; N, 5.33.

5,5-Dimethoxy-5,5-dihydro-8-isoquinolinone (**6**)

To a solution of 4.37 g (17.4 mmol) of diketal (**9**) in 155 mL of acetone were added 155 mL of 2% aqueous acetic acid. After stirring for 45 min at 50°C the mixture was concentrated *in vacuo* and the

residue was dissolved in ether. The ethereal solution was washed with water and dried over anhydrous $MgSO_4$ and evaporated to afford 3.03 g (85%) of **6**. The crude product can be used for the next reaction step without further purification. For spectroscopic purposes a small sample was purified by TLC (silica gel, ethyl acetate/light petroleum 7/3, 1% NEt_3) furnishing a semicrystallinic mass. IR (NaCl, liquid film): cm^{-1} 2944, 2834, 1682, 1592; MS: *m/z* (%) 205 (M^++1, 4), 174 (100), 146 (39), 131 (16), 117 (79; 103 (13), 76 (16), 50 (19); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.25 (s, 6H, OMe), 6.60 (d, *J* = 10.6 Hz, 1H, H-7), 7.01 (d, *J* = 10.6 Hz, 1H, H-6), 7.62 (dd, *J* = 5.2 Hz and 0.9 Hz, 1H, H-4), 8.87 (d, *J* = 5.2 Hz, 1H, H-3), 9.27 (d, *J* = 0.9 Hz, 1H, H-1); ^{13}C-NMR ($CDCl_3$): δ (ppm) 51.3 (OMe), 93.7 (C-5), 120.5 (C-4), 125.8 (C-8a), 132.4 (C-7), 143.4 (C-6), 147.4 (C-4a), 148.8 (C-1), 153.8 (C-3), 183.0 (C-8). HRMS: Calcd for $C_{11}H_{11}NO_3$: 205.07389. Found: 205.074±0.001. *Anal.* Calcd. for $C_{11}H_{11}NO_3.0.1H_2O$: C, 63.82; H, 5.45; N, 6.77. Found: C, 63.60; H, 5.62; N, 6.41.

4,9-Dihydro-2*H*-pyrrolo[3,4-*g*]isoquinoline-4,9-dione (**1**)

Compound (**6**) (3.0 g, 14.7 mmol) and 2.88 g (14.7 mmol) of tosylmethyl isocyanide were dissolved in 18 mL of dry THF under Ar atmosphere. Under vigorous stirring 2.0 g (18.0 mmol) of potassium *tert*.-butoxide in 18 mL of dry THF were added and the mixture was stirred for 18 h at rt. After addition of water the mixture was exhaustively extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in 370 mL of acetone and 46 mL of water. To this mixture 3.0 g (12 mmol) of pyridinium *p*-toluenesulfonate (PPTS) and 0.346 g (1.65 mmol) of pyridinum *p*-toluenesulfonic acid hydrate were added at rt. After stirring for 18 h the mixture was diluted with 465 mL of ethyl acetate, washed with brine (465 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The solid residue (2.37 g) was rectified by column chromatography (aluminium oxide, eluent: gradient ethyl acetate $\rightarrow$ ethyl acetate/methanol 9/1) furnishing 0.963 g (33%) of yellow crystals (mp undef. > 300°C decomp; ethyl acetate/methanol). IR (KBr): cm^{-1} 3079, 2964, 1664, 1592; MS: *m/z* (%) 198 (M^++1, 100), 170 (29), 142 (21), 115 (29), 87 (17), 77 (7), 66 (17), 50 (28); ^{1}H-NMR (DMSO-d_6): δ (ppm) 7.76 and 7.80 (AB-system, *J* = 1.6 Hz, each 1H, H-1 and H-3)[18],7.92 (dd, *J* = 4.9 Hz and 0.8 Hz, 1H, H-8), 9.01 (d, *J* = 4.9 Hz, 1H, H-7), 9.25 (d, *J* = 0.8 Hz, 1H, H-5), 12.70 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 118.9 (C-8, ^1J = 168.2 Hz, ^2J = 8.9 Hz, ^4J = 1.5 Hz), 121.3 (C-3a and C-9a), 123.1 (^1J = 192.4 Hz, ^3J = 7.2 Hz) and 124.1 (^1J = 192.4 Hz, ^3J = 7.2 Hz) (C-1 and C-3),[18] 127.8 (C-4a), 140.6 (C-8a), 148.3 (C-5, ^1J = 183.4 Hz, ^3J = 11.4 Hz), 154.7 (C-7, ^1J = 182.5 Hz, ^2J = 3.2 Hz, ^3J = 11.8 Hz), 178.4 (C-9), 179.0 (C-4). HRMS: Calcd for $C_{11}H_6N_2O_2$: 198.0429. Found: 198.043±0.001. *Anal.* Calcd for $C_{11}H_6N_2O_2.0.3H_2O$: C, 64.90; H, 3.27; N, 13.76. Found: C, 64.91; H, 3.26; N, 13.58.

Methyl 4-[[1-(1,1,1-Triisopropylsilyl)-1*H*-3-pyrrolyl]carbonyl]nicotinate (**13**)

To a suspension of 17.6 g (132 mmol) of aluminium trichloride in 377 mL of dry CH_2Cl_2 was added under Ar atmosphere 9.84 g (66 mmol) of pyridine-3,4-dicarboxylic acid anhydride (**10**). After stirring for 30 min at rt a solution of 4.1 g (18.3 mmol) of 1-(1,1,1-triisopropylsilyl)-1*H*-pyrrole in 75 mL of dry CH_2Cl_2 was added dropwise and the stirring was continued for further 18 h at rt. Afterwards the mixture was cooled to 0°C and hydrolyzed by addition of crushed ice. The resulting thick mass was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* thus affording 6.77 g (27%) of acid (**12**) of mp 163-165°C (water). The crude acid was suspended in methanol and treated at rt by dropwise addition with an ethereal solution of diazomethane. After complete reaction the mixture was evaporated to dryness. The residue was dissolved in CH_2Cl_2 and extracted with water. After drying over anhydrous $MgSO_4$ the organic solvent was evaporated under diminished pressure. Yield 6.6 g (94 %). A sample was purified for spectroscopic purposes by TLC (silica gel, ethyl acetate/light petroleum) thus obtaining colorless crystals of mp 140-141°C (ethyl acetate/light petroleum). IR: cm^{-1} 1723,1645, 1585. MS: *m/z* (%) 386 (M^+, 3), 343 (11), 198 (100), 170 (17), 142 (52), 115 (36), 94 (27), 77 (34). ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.07 (d, *J* = 7.5 Hz, 18H, C-Me), 1.42 (septet, *J* = 7.5 Hz, 3H, CH of isopropyl), 3.69 (s, 3H, OMe), 6.61 (dd, *J* = 2.9 Hz and 1.5 Hz, 1H, pyrrole H-4), 6.76 (dd, *J* = 2.9 Hz and 2.1 Hz, 1H, pyrrole H-5), 7.07 (dd, *J* = 2.1 Hz and 1.5 Hz, 1H, pyrrole H-2), 7.37 (dd, *J* = 5.0 Hz and 0.7 Hz, 1H, pyridine H-5), 8.82 (d, *J* = 5.0 Hz, pyridine H-6), 9.18 (d, *J* = 0.7 Hz, 1H, pyridine H-2); ^{13}C-NMR ($CDCl_3$): δ (ppm) 11.5 ($\underline{C}HMe_2$), 17.6 ($CH\underline{Me}_2$), 52.3 (OMe), 111.3 (pyrrole C-4), 121.6 (pyridine C-5), 124.2 (pyridine C-3), 126.2 (pyrrole C-5), 127.1 (pyrrole C-3), 131.5 (pyrrole C-2), 149.7 (pyridine C-4), 151.2 (pyridine C-2), 153.0 (pyridine C-6), 165.4 (COO), 189.0 (CO). HRMS: Calcd for $C_{21}H_{30}N_2O_3Si$: 386.2026. Found: 386.203±0.005. *Anal.* Calcd for $C_{21}H_{30}N_2O_3Si$: C, 65.25; H, 7.82; N, 7.25. Found: C, 65.08; H, 7.64; N, 7.36.

Methyl 4-(1*H*-3-pyrrolylcarbonyl)nicotinate (**14**)

A solution of 6.6 g (17 mmol) of **13** in 125 mL dry acetonitrile was added under Ar atmosphere to 17 mL (17 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF by drowise addition. After stirring for 5 min the mixture was diluted with ethyl acetate, washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* thus obtaining 7.19 g residue (containing a mixture of **14** and triisopropylsilanol). Purification for spectroscopic purposes was carried out by TLC (silica gel, ethyl acetate/light petroleum 6/4) affording colorless crystals of mp 151-152°C (ethyl acetate/light petroleum). IR (KBr): cm^{-1} 3252, 1729, 1633; MS: *m/z* (%) 231 (M^++1, 1), 230 (M^+, 9), 199 (3), 95 (6), 94 (100), 78 (2), 66(14), 61 (2); ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.66 (s, 3H, OMe), 6.44 (m, 1H, pyrrole H-4), 6.89 (m, 1H, pyrrole H-5), 7.15 (m, 1H, pyrrole H-2), 7.47 (d, *J* = 4.9 Hz, 1H, pyridine H-5), 8.84 (d, *J* = 4.9 Hz,

1H, pyridine H-6), 9.03 (s, 1H, pyridine H-2), 11.62 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 52.3 (OMe), 108.1 (pyrrole C-4), 120.7 (pyrrole C-5), 121.7 (pyridine C-5), 123.8 (pyrrole C-3), 123.9 (pyridine C-3), 126.5 (pyrrole C-2), 149.2 (pyridine C-4), 150.2 (pyridine C-2), 153.0 (pyridine C-6), 165.2 (COO), 187.8 (CO). HRMS: Calcd for $C_{12}H_{10}N_2O_3$: 230.06914. Found: 230.069±0.005. *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.35; H, 4.41; N, 11.96.

Methyl 4-[[1-phenylsulfonyl-1*H*-3-pyrrolyl]carbonyl]nicotinate (**15**)

To a vigorously stirred mixture of 7.19 g of the residue of the previously described reaction and 0.577 g (1.7 mmol) of tetrabutyl ammoniumsulfate in 8.5 mL of 50% aqueous NaOH and 85 mL of CH_2Cl_2 was added under Ar-atmosphere at rt a solution of 5.28 g (29.9 mmol) of benzenesulfonyl chloride in 8.5 mL of CH_2Cl_2 by dropwise addition. After stirring for 30 min the mixture was diluted with CH_2Cl_2 and washed with water. Drying over anhydrous $MgSO_4$ and concentration *in vacuo* afforded crude **18** which was purified by column chromatography (silica gel, ethyl acetate/light petroleum 6/4). Yield: 4.76 g (75 %) of colorless crystals of mp 128°C (ethyl acetate/light petroleum). IR (KBr): cm^{-1} 3125, 1726, 1669, 1584, 1550, 1372, 1178, 1076; MS: *m/z* (%) 370 (M^+, 8), 234 (32), 141 (16), 93 (10), 78 (12), 77 (100), 69 (19); ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.57 (s, 3H, OMe), 6.70 (dd, *J* = 3.4 Hz and 1.6 Hz, 1H, pyrrole H-4), 7.53 (m, 2H, pyrrole H-5, pyridine H-5), 7.66 (m, 2H, Ph H-3,5), 7.75 (m, 1H, pyrrole H-2), 7.80 m, 1H, Ph H-4), 8.06 (m, 2H, Ph H-2,6), 8.90 (d, *J* = 5.0 Hz, pyridine H-6), 9.09 (s, 1H, pyridine H-2); ^{13}C-NMR (DMSO): δ (ppm) 52.5 (OMe), 112.3 (pyrrole C-4), 121.6 (pyridine C-5), 123.0 (pyrrole C-5), 123.3 (pyridine C-3), 127.0 (pyrrole C-2), 127.4 (Ph C-2,6), 127.9 (pyrrole C-3), 130.2 (Ph C-3,5), 135.4 (Ph C-4), 137.0 (Ph C-1), 147.9 (pyridine C-4) 150.6 (pyridine C-2), 153.7 (pyridine C-6), 164.8 (COO), 188.4 (CO). HRMS: Calcd for $C_{18}H_{14}O_5N_2S$: 370.0623. Found: 370.0635±0.005. *Anal.* Calcd for $C_{18}H_{14}O_5N_2S$: C, 58.37; H, 3.81; N, 7.56. Found: C, 58.41; H, 3.73; N, 7.38.

4,9-Dihydro-1*H*-pyrrolo[3,2-*g*]isoquinoline-4,9-dione (**2**)

A solution of 4.76 g (12.9 mmol) of **14** in 400 mL dry. THF was added slowly at -76°C under Ar atmosphere to 31.8 mL (31.8 mmol) of a 1 M solution of lithium bis(trimethylsilyl)amide in THF. After the mixture was allowed to warm up to -40°C the reaction was completed at this temperature (DC monitoring). The solvent was distilled off under diminished pressure and the residue was treated with saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic extractes were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue (3.99 g, 11.8 mmol) and 3.35 g (24.2 mmol) of potassium carbonate were dissolved in 90 mL methanol/water (2/1) and refluxed for 5 h. Subsequently, the mixture was diluted with water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography

(silica gel, ethyl acetate) to afford 701 mg (27 %) of yellow crystals of mp 290°C (decomp.; ethyl acetate). IR (KBr): cm^{-1} 3034, 2921, 1657, 1558; MS: *m/z* (%) 199 (M^++1, 13), 198 (M^+, 100), 170 (62), 142 (49), 115 (32), 114 (15), 87 (16), 78 (12); ^{1}H-NMR (DMSO-d_6): δ (ppm) 6.71 (d, *J* = 2.7 Hz, 1H, H-3), 7.39 (d, *J* = 2.7 Hz, 1H, H-2), 7.85 (d, *J* = 5.0 Hz, 1H, H-5), 9.00 (d, *J* = 5.0 Hz, 1H, H-6), 9.15 (s, 1H, H-8), 13.07 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 108.3 (C-3), 118.7 (C-5), 126.0 (C-8a), 126.9 (C-3a), 128.4 (C-2), 132.0 (C-9a), 139.2 (C-4a), 147.2 (C-8), 155.2 (C-6), 174.2 (C-9), 179.3 (C-4). HRMS: Calcd for $C_{11}H_6N_2O_2$: 198.0429. Found: 198.0434±0.005. *Anal.* Calcd for $C_{11}H_6N_2O_2.0.3H_2O$: C, 64.90; H, 3.27; N, 13.76. Found: C, 64.73; H, 3.33; N, 13.31.

Methyl 3-[[1-(1,1,1-Triisopropylsilyl)-1*H*-3-pyrrolyl]carbonyl]nicotate (**17**)

To a suspension of 6.0 g (45 mmol) of aluminium trichloride in 124 mL of dry CH_2Cl_2 was added under Ar atmosphere a solution of 4.45 g (22.3 mmol) of methyl 3-chlorocarbonyl isonicotinate (**16**).[16] After stirring for 10 min at rt a solution of 2.52 g (11.3 mmol) of 1-(1,1,1-triisopropylsilyl)-1*H*-pyrrole in 30 mL of dry CH_2Cl_2 was added dropwise and the stirring was continued for further 18 h at rt. Afterwards the mixture was cooled to 0°C and hydrolyzed by addition of crushed ice. After separation of the phases the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford 5.50 g (79 %) of crude **17** as dark colored oil), which can be used for the next reaction step without any further purification. A sample was purified for spectroscopic purposes by TLC (light petroleum/ethyl acetate 7/3) affording colorless crystals of mp 72-73°C (ethyl acetate/light petroleum). IR (KBr): 1727, 1643, 1526; MS: *m/z* (%) 386 (M^+, 7), 343 (26), 164 (48), 131 (23), 103 (38), 84 (38), 75 (100), 59 (56); ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.05 (d, *J* = 7.4 Hz, 18H, CH$\underline{Me}_2$), 1.40 (septet, J = 7.4 Hz, 3H, C$\underline{H}Me_2$), 3.67 (s, 3H, OMe), 6.65 (dd, *J* = 2.9 Hz and 1.5 Hz, 1H, pyrrole H-4), 6.75 (dd, *J* = 2.9 Hz and 2.0 Hz, 1H, pyrrole H-5), 7.10 (dd, *J* = 2.0 Hz and 1.5 Hz, 1H, pyrrole H-2), 7.71 (dd, *J* = 5.0 Hz and 0.7 Hz, 1H, pyridine H-5), 8.80 (m, 2H, pyridine H-2, pyridine H-6); ^{13}C-NMR ($CDCl_3$): δ (ppm) 11.4 ($\underline{C}HMe_2$), 17.5 (CH$\underline{Me}_2$), 52.5 (OMe), 111.4 (pyrrole C-4), 122.6 (pyridine C-5), 126.1 (pyrrole C-5), 127.8 (pyrrole C-3), 131.5 (pyrrole C-2), 136.0 (pyridine C-3), 137.4 (pyridine C-4), 149.1 (pyridine C-2), 151.1 (pyridine C-6), 166.0 (COO), 188.5 (CO). HRMS: Calcd for $C_{21}H_{30}N_2O_3Si$:386.2026. Found: 386.202±0.005. *Anal.* Calcd for $C_{21}H_{30}N_2O_3Si$: C, 65.95; H, 7.82; N, 7.25. Found: C, 64.98; H, 7.56; N, 7.21.

Methyl 3-(1*H*-3-pyrrolylcarbonyl)nicotinate (**18**)

Compound (**17**) (5.50 g, 14.2 mmol) was converted to **18** in the same way as described for the synthesis of **14** to afford 3.53 g residue (containing a mixture of **18** and triisopropylsilanol). A sample was purified for spectroscopic purposes by TLC (ethyl acetate) affording colorless crystals of mp 105-108°C (ethyl

acetate). IR (KBr): cm^{-1} 3147, 1732, 1635, 1586; MS: *m/z* (%) 230 (M^+, 13), 199 (4), 95 (8), 94 (100), 86 (36), 84 (52), 69 (13), 66 (19); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.72 (s, 3H, OMe), 6.61 (m, 1H, pyrrole H-4), 6.78 (m, 1H, pyrrole H-5), 7.09 (m, 1H, pyrrole H-2), 7.74 (d, *J* = 5.0 Hz, 1H, pyridine H-5), 8.77 (s, 1H, pyridine H-2), 8.80 (d, *J* = 5.0 Hz, 1H, pyridine H-6), 9.66 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 52.8 (OMe), 109.3 (pyrrole C-4), 120.4 (pyrrole C-5), 122.9 (pyridine C-5), 125.4 (pyrrole C-3), 126.0 (pyrrole C-2), 136.1 (pyridine C-3), 137.3 (pyridine C-4), 148.8 (pyridine C-2), 151.1 (pyridine C-6), 165.9 (COO), 188.9 (CO). HRMS: Calcd for $C_{12}H_{10}N_2O_3$:230.0691. Found: 230.0701±0.005. *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.87; H, 4.67; N, 11.92.

Methyl 3-[[1-phenylsulfonyl-1H-3-pyrrolyl]carbonyl]nicotinate (**19**)

The crude residue of the previously described reaction was converted to the sulfonated product (**19**) in the same way as described for the synthesis of compound (**15**). Purification by column chromatography (silica gel, ethyl acetate/light petroleuem 2/1) afforded 0.90 g (17 %) of colorless crystals of mp 119-120°C (ethyl acetate/light petroleum). IR (KBr): cm^{-1} 3113, 1718, 1667, 1582; MS: *m/z* (%) 370 (M^+, 9), 234 (22), 141 (16), 86 (67), 84 (100), 77 (78), 59 (34); ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.58 (s, 3H, OMe), 6.67 (dd, *J* = 3.3 Hz and 1.5 Hz, 1H, pyrrole H-4), 7.14 (dd, *J* = 3.3 Hz and 2.3 Hz, 1H, pyrrole H-5), 7.36 (dd, *J* = 2.3 Hz and 1.5 Hz, 1H, pyrrole H-2), 7.50 (m, 2H, Ph H-3,5), 7.61 (m, 1H, Ph H-4), 7.72 (d, *J* = 5.0 Hz, 1H, pyridine H-5), 7.84 (m, 2H, Ph H-2,6), 8.68 (s, 1H, pyridine H-2), 8.81 (d, *J* = 5.0 Hz, 1H, pyridine H-6); ^{13}C-NMR ($CDCl_3$) δ (ppm) 53.2 (OMe), 113.1 (pyrrole C-4), 122.6 (pyrrole C-5), 123.4 (pyridine C-5), 126.4 (pyrrole C-2), 127.6 (Ph C-2,6), 129.4 (pyrrole C-3), 130.2 (Ph C-3,5), 135.1 (Ph C-4), 137.4 and 138.1 (Ph C-1, pyridine C-3, pyridine C-4),[18] 149.0 (pyridine C-2), 152.3 (pyridine C-6), 165.7 (COO), 188.6 (CO). HRMS: Calcd for $C_{18}H_{14}O_5N_2S$: 370.0623. Found: 370.0629±0.005. *Anal.* Calcd for $C_{18}H_{14}O_5N_2S$: C, 58.37; H, 3.81; N, 7.56. Found: C, 58.62; H, 3.97; N, 7.45.

4,9-Dihydro-1*H*-pyrrolo[2,3-*g*]isoquinoline-4,9-dione (**3**)

Compound (**19**) (0.88 g, 2.4 mmol) was converted into pyrrole derivative (**3**) in the same way as described for the synthesis of compound (**2**). Yield: 0.305 g (65 %) of yellow crystals of mp 250°C (decomp., ethyl acetate). IR (KBr): 3035, 2762, 1660, 1590; MS: *m/z* (%) 198 (M^+, 100), 197 (79; 183 (7), 170 (34), 142 (17), 115 (11); ^{1}H-NMR (DMSO-d_6): δ (ppm) 6.69 (d, *J* = 2.7 Hz, 1H, H-3), 7.42 (d, *J* = 2.7 Hz, 1H, H-2), 7.85 (d, *J* = 4.9 Hz, 1H, H-8), 8.99 (d, *J* = 4.9 Hz, 1H, H-7), 9.13 (s, 1H, H-5), 13.09 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 108.2 (C-3, ^1J = 177.4 Hz, ^2J = 8.5 Hz), 118.4 (C-8, ^1J = 168.4 Hz, ^2J = 9.1 Hz, ^4J = 1.5 Hz), 126.2 (C-4a), 127.1 (C-3a), 129.0 (C-2, ^1J = 189.4 Hz, ^2J = 8.3 Hz), 131.9 (C-9a), 138.9 (C-8a), 147.4 (C-5, ^1J = 183.5 Hz, ^3J = 11.5 Hz), 155.1 (C-7, ^1J = 183.0 Hz, ^2J = 3.1

Hz, ^{3}J = 11.8 Hz), 173.4 (C-9), 180.0 (C-4). HRMS: Calcd for $C_{11}H_6N_2O_2$:198.0429. Found: 198.0435 ±0.005. *Anal.* Calcd for $C_{11}H_6N_2O_2$: C, 66.67; H, 3.05; N, 14.14. Found: C, 66.37; H, 3.29; N, 13.98.

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18. Assignments of the indicated resonances within one spectrum may be interchanged.