Synthesis of 3-Aminopyrrolo[2,1-*a*]isoquinoline, 3-Aminopyrrolo[2,1-*a*]phthalazine, and 7-Aminopyrrolo[1,2-*b*]pyridazine Derivatives

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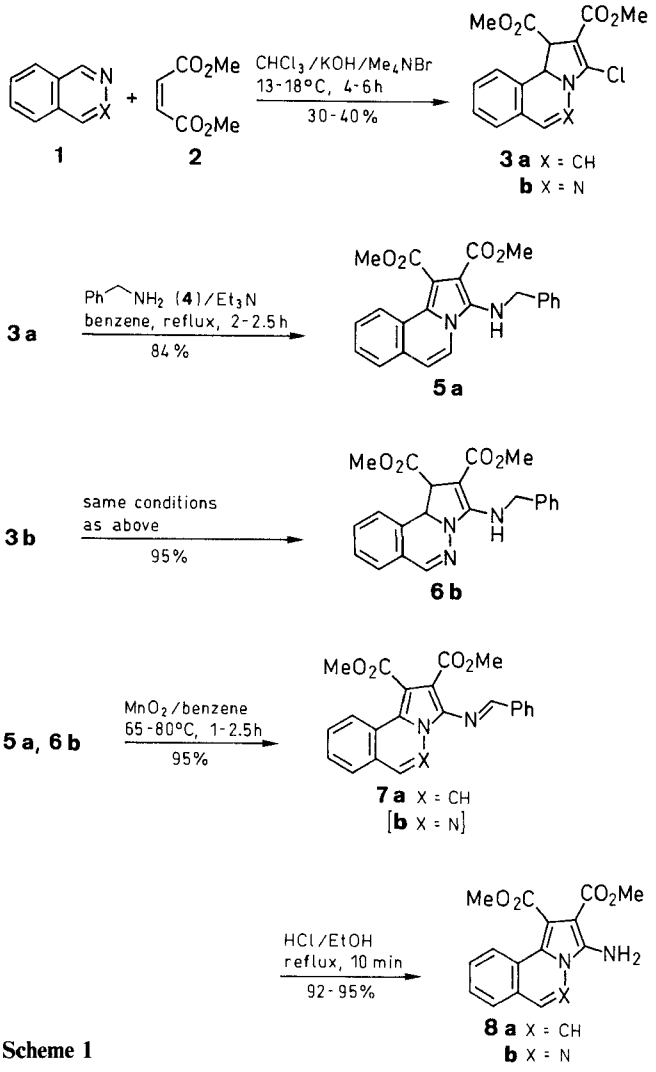
A simple route to 3-aminopyrrolo[2,1-*a*]isoquinoline, 3-aminopyrrolo[2,1-*a*]phthalazine, and 7-aminopyrrolo[1,2-*b*]pyridazine derivatives **8a, 8b** and **11**, respectively, is described, based on displacement of a chlorine atom in the appropriate precursors with benzylamine. The chloro-substituted precursors were prepared by using a tandem dichlorocarbene/cycloimmonium ylide approach.

Alkyl aminopyrrolecarboxylates have proved to be useful building blocks for the synthesis of a wide range of fused heterocyclic systems.[1] However, 3-aminoindolizine analogues are not readily available. To our knowledge, no synthesis of 3-aminopyrrolo[2,1-*a*]isoquinoline, 3-aminopyrrolo[2,1-*a*]phthalazine, and 7-aminopyrrolo[1,2-*b*]-pyridazine derivatives has appeared in the literature.

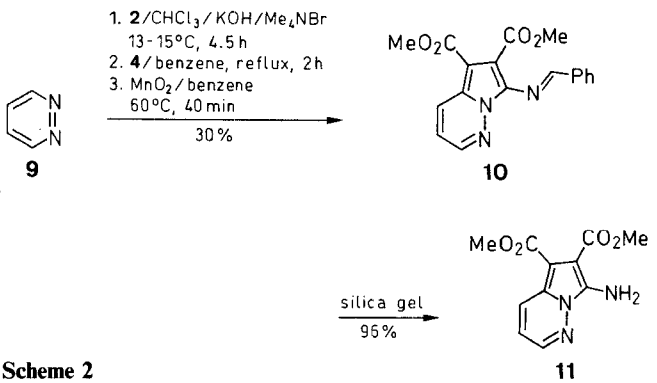
We report here a convenient procedure for the synthesis of dimethyl 3-aminopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate **(8a)**, dimethyl 3-aminopyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate **(8b)**, and dimethyl 7-aminopyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate **(11)** involving substitution of chlorine in the appropriate chloro-substituted precursors.

The precursors **3a,b** and dimethyl 7-chloro-4a,5-dihydropyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate were prepared by using a carbene method of generation of cycloimmonium dichloromethylide,[2-5] which then undergoes a 1,3-dipolar cycloaddition with **2**.[2,3] Dichlorocarbene was generated by the reaction of chloroform with potassium hydroxide powder in the presence of trimethylammonium bromide as a phase-transfer catalyst. Under the above conditions less resin was formed in the reaction mixture, in comparison to those using sodium hydroxide, and benzyltriethylammonium chloride as the phase-transfer catalyst.[3] The reaction of dichlorocarbene with azines **1a,b** leads to the azinium dichloromethylides, which are intercepted with **2** to give the corresponding substituted dichlorotetrahydropyrroloazines. Under the reaction conditions the latter undergoes dehydrochlorination to give **3a,b** (Scheme 1). Pyrroline derivatives **3a,b** were stable in dilute solution or in the crystalline state for 1–2 days. When storing **3a,b** for a longer time, a resin was formed and partial conversion of the compounds to the corresponding aromatic pyrroloazines had occurred.



Scheme 1

When a solution of **3a** and benzylamine **(4)** was heated under reflux, the aromatic compound **5a** was isolated in high yield. However, nonaromatic compound **6b** was obtained from **3b** under these conditions (Scheme 1). Compound **6b** underwent aromatization on heating with manganese dioxide to afford **5b**. Benzylamines **5a** and **6b** were oxidized by activated manganese dioxide by heating in benzene solution to give azomethines **7a,b**. Hydrolysis of **7a,b** proceeded successfully in the presence of hydrochloric acid to afford compounds **8a,b** in 90–95% yield (Scheme 1). A similar sequence of reactions was performed, starting from pyridazine **9**, (without special purification and characterization of intermediate products) to give azomethine **10**. The compound **10** was hydrolyzed during chromatography on silica gel to give amine **11** in near quantitative yield (Scheme 2).



Scheme 2

However, the above approach is not applicable when 1,3-dipolar cycloaddition of cycloimmonium dichloromethylide leads to dichlorotetrahydropyrroloazine, which easily undergoes dehydrochlorination and aromatization under the reaction conditions (cf. Ref. 3). In this case, no displacement of chlorine atom by benzylamine occurred, as was shown by special experiment with dimethyl 3-chloropyrrolo[1,2-*a*]isoquinoline-1,2-dicarboxylate.

All new products were characterized by ^{1}H NMR, IR, and UV spectra as well as elemental analyses.

All reagent were of commercial origin and freshly distilled or crystallized before use. Activated MnO_2 was prepared according to Attenborrow at al.[6] Reagent quality solvents were, except for $CHCl_3$, used without further purification. $CHCl_3$ was purified according to literature procedure.[7] Melting points were determined with a hot stage microscope (Boetius) and are uncorrected. Microanalyses were obtained using a Hewlett-Packard 185B CHN-analyser. TLC was carried out on plates SILUFOL^R UV_{254} (Kavalier, Czechoslovakia). Column chromatography separations were performed on silica gel L 100/160 (100–160 μm), (Lachema, Czechoslovakia). IR spectra were obtained on Carl-Zeiss UR-20 spectrophotometer and UV spectra on Carl Zeiss Specord M-40. ^{1}H NMR spectra were recorded on a Tesla-567A (100 MHz) spectrometer.

Dimethyl 3-Chloro-1,4a-dihydropyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (3a):
A mixture of isoquinoline (**1a**; 0.64 g, 5 mmol), dimethyl maleate (**2**; 1.44 g, 10 mmol), Me_4NBr (0.154 g, 1 mmol), and powdered KOH (0.84 g, 15 mmol) in $CHCl_3$ (50 mL) was stirred efficiently at 18 °C under Ar for 1.5 h and then additional powdered KOH (0.84 g, 15 mmol) was added in 3 h. The precipitate was separated by filtration, washed with $CHCl_3$ (3 × 5 mL), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 20% EtOAc/hexane as eluent. The compound **3a** obtained was used without additional purification for the next step. In order to determine the yield of the above step, a separate experiment was conducted. After the workup, the solvent was removed and the residue was crystallized from Et_2O; yield: 0.48 g (30%); mp 95–97 °C (Lit.[3] mp 95–97 °C).

Dimethyl 3-(Benzylamino)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (5a):
To a stirred solution of **3a** (~ 1.5 mmol) from the above reaction in benzene (15 mL) under Ar were added benzylamine (**4**; 0.48 g, 4.5 mmol) and Et_3N (0.46 g, 4.5 mmol). The mixture was refluxed for 4 h. Precipitated amine hydrochlorides were filtered and the precipitate was washed with benzene (3 × 5 mL). Benzene was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (20 mL). The solution was shaken with conc. HCl (0.5 mL), followed by H_2O (20 mL). The layers were separated and the organic layer was washed with 5% aq Na_2CO_3 (10 mL) followed by H_2O (10 mL), and dried ($MgSO_4$). The solvent was evaporated on a rotary evaporator in vacuo and the residue was crystallized from Et_2O; yellow needles; yield: 0.49 g (84%); mp 125.5–127 °C.

$C_{23}H_{20}N_2O_4$	calc.	C 71.12	H 5.19	N 7.21
(319.8)	found	71.10	5.18	7.17

IR ($CHCl_3$): ν = 3350, 1725, 1705 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 209 (4.67), 276 (4.72), 340 nm (4.03).

^{1}H NMR ($CDCl_3$/HMDS): δ = 3.75 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.18 (d, 2H, J = 7 Hz, CH_2), 5.30 (m, 1H, NH), 6.75 (d, 1H, J = 7.4 Hz, H-6), 7.30–7.51 (m, 8H, C_6H_5 + H-7, 8, 9), 7.72 (d, 1H, J = 7.4 Hz, H-5), 8.24 (dd, 1H, J = 6, 2.5 Hz, H-10).

Dimethyl 3-(Benzylidenamino)pyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (7a):
To a solution of **5a** (0.49 g, 1.26 mmol) in benzene (20 mL) was added activated MnO_2 (3 g, 35 mmol) and the suspension was stirred vigorously at 80 °C for 1 h. The precipitate was separated by filtration, washed with $CHCl_3$ until the washings were colorless and the filtrate was evaporated to dryness in vacuo. The crude product was recrystallized from EtOH to give bright yellow needles; yield: 0.464 g (95%); mp 161–162.5 °C.

$C_{23}H_{18}N_2O_4$	calc.	C 71.49	H 4.70	N 7.25
(386.4)	found	71.45	4.81	7.03

IR ($CHCl_3$): ν = 1720 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 205 (4.79), 278 (4.87), 403 nm (4.37)

^{1}H NMR ($CDCl_3$/HMDS): δ = 3.82 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.81 (d, 1H, J = 7.5 Hz, H-6), 7.26–7.46 (m, 6H, 3H$_{arom}$ + H-7, 8, 9), 7.87–7.97 (m, 2H$_{arom}$), 8.11 (d, 1H, J = 7.5 Hz, H-5), 8.56 (dd, 1H, J = 5.6, 2.5 Hz, H-10), 8.98 (s, 1H, =CH).

Dimethyl 3-Aminopyrrolo[2,1-*a*]isoquinoline-1,2-dicarboxylate (8a):
Compound **7a** (0.464 g, 1.2 mmol) was dissolved in a minimum volume of hot EtOH. To the solution was added conc. HCl (0.15 mL) and the mixture was refluxed for ca. 10 min. After disappearance of the starting compound **7a** (TLC control, 20% EtOAc/hexane as eluent), sat. aq $NaHSO_3$ was added dropwise to the cooled (r.t.) mixture shaking periodically until precipitation of bisulfite derivative of benzaldehyde was over. The precipitate was separated by filtration, washed with EtOH (2 × 2 mL) and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in benzene (15 mL), the solution was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo. Recrystallization of the residue from benzene afforded pure **8a** as pale yellow needles; yield: 0.328 g (92%); mp 156–157 °C.

$C_{16}H_{14}N_2O_4$	calc.	C 64.42	H 4.73	N 9.39
(298.3)	found	64.42	4.74	9.30

IR ($CHCl_3$): ν = 3440, 3350, 1725, 1695 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 211 (4.21), 267 (4.57), 356 nm (3.99).

^{1}H NMR ($CDCl_3$/HMDS): δ = 3.78 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.05 (br m, 2H, NH_2), 6.30 (d, 1H, J = 7.7 Hz, H-6), 7.09–7.40 (m, 3H, H-7, 8, 9), 7.31 (d, 1H, J = 7.7 Hz, H-5), 7.89 (d, 1H, J = 7.4 Hz, H-10).

Dimethyl 3-Chloro-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (3b):
A mixture of phthalazine (**1b**; 1 g, 7.7 mmol), dimethyl maleate (**2**; 2.22 g, 15.4 mmol), Me_4NBr (0.237 g, 1.5 mmol), and powdered KOH (1.29 g, 23 mmol) in $CHCl_3$ (50 mL) was stirred vigorously at 13–15 °C under Ar for 1.5 h, and then additional powdered KOH (0.84 g, 15 mmol) was added in 4.5 h. The precipitate was separated by filtration, washed with $CHCl_3$ (3 × 5 mL), and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 28% EtOAc/hexane as eluent. Recrystallization of the product from Et_2O afforded pure **3b**; yield: 0.992 g (40%); mp 115–116 °C.

$C_{15}H_{13}ClN_2O_4$	calc.	C 56.17	H 4.08	N 8.73
(320.7)	found	56.22	4.19	8.80

IR ($CHCl_3$): ν = 1745, 1700 cm^{-1}.

^{1}H NMR ($CDCl_3$/HMDS): δ = 3.51 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.29 (d, 1H, J = 10 Hz, H-1), 5.25 (d, 1H, J = 10 Hz, H-10b), 7.21–7.46 (m, 4H, H-7 to 10), 7.47 (s, 1H, H-6).

Dimethyl 3-(Benzylamino-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (6b):
To a stirred solution of **3b** (0.992 g, 3.1 mmol) in benzene (30 mL) under Ar were added benzylamine (**4**; 0.332 g, 3.1 mmol) and Et_3N (0.94 g, 9.3 mmol). The mixture was refluxed for 3 h. Precipitated amine hydrochlorides were filtered and the precipitate was washed with benzene (3 × 5 mL). The filtrate was concentrated (30 mL), washed with 0.1 N aq HCl (2 × 30 mL) (to remove unconsumed amines), followed by H_2O (15 mL), dried (Na_2SO_4), and evaporated in vacuo. Recrystallization of the residue from Et_2O afforded pure **6b** as pale green-yellow prisms; yield: 1.15 g (95%); mp 120–122 °C.

$C_{22}H_{21}N_3O_4$	calc.	C 67.51	H 5.41	N 10.74
(391.4)	found	67.76	5.59	11.01

IR ($CHCl_3$): ν = 3300, 1740, 1665 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 254 (4.22), 286 (4.33), 373 nm (4.18).

^1H NMR ($CDCl_3$/HMDS): δ = 3.40 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 4.07 (d, 1 H, J = 8.4 Hz, H-1), 4.94 (d, 2 H, J = 6.5 Hz, CH_2), 5.13 (d, 1 H, J = 8.4 Hz, H-10b), 7.15–7.36 (m, 10 H, Ph, H-6 to 10, 10-H), 7.88 (br t, 1 H, J = 6.5 Hz, NH).

Dimethyl 3-Aminopyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (8b):
To a solution of **6b** (1.15 g, 2.94 mmol) in benzene (20 mL) was added activated MnO_2 (10 g, 115 mmol) and the suspension was efficiently stirred at 65 °C for 2.5 h. The precipitate was separated by filtration and washed with $CHCl_3$ until the washings were colorless. The filtrate was evaporated to dryness in vacuo, giving a crude mixture of **7b** and **8b**. This mixture was dissolved in hot EtOH (179 mL). To the solution was added conc. HCl (7 drops) and the mixture was refluxed for 7 min. After cooling, the product started to precipitate, the mixture was allowed to stand at 0 °C until crystallization was complete. The product was filtered and recrystallized from CH_2Cl_2; orange needles; yield: 0.835 g (95 %); mp 228–229 °C.

$C_{15}H_{13}N_3O_4$	calc.	C 60.20	H 4.38	N 14.04
(299.3)	found	59.96	4.39	14.07

IR ($CHCl_3$): ν = 3490, 3380, 1720, 1690 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 210 (4.60), 279 (4.52), 295 (4.54), 353 nm (4.06).

^1H NMR ($CDCl_3$/HMDS): δ = 3.85 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 5.61 (br s, 2 H, NH_2), 7.27–7.66 (m, 3 H, H-7, 8, 9), 8.12 (d, 1 H, J = 7 Hz, H-10), 8.14 (s, 1 H, H-6).

Dimethyl 3-(Benzylamino)pyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (5b):
An experiment similar to the one described above was carried out with **6b** (1.05 g, 2.68 mmol) and activated MnO_2 (5 g, 58 mmol) for 1 h, affording a mixture of **5b**, **7b**, and **8b**. Pure sample of **5b** was obtained by column chromatography on silica gel using 20 % EtOAc/hexane mixed solvent as eluent, followed by recrystallization from Et_2O; yield: 0.32 g (31 %); yellow needles; mp 124–127 °C.

$C_{22}H_{19}N_3O_4$	calc.	C 67.86	H 4.92	N 10.79
(389.4)	found	67.79	4.94	10.68

IR ($CDCl_3$): ν = 3345, 1720, 1690 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 211 (4.95), 281 (4.91), 349 nm (4.33).

^1H NMR ($CDCl_3$/HMDS): δ = 3.78 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.81 (d, 2 H, J = 6.7 Hz, CH_2), 6.43 (br t, 1 H, J = 6.7 Hz, NH), 7.21–7.61 (m, 8 H, Ph, H-7, 8, 9), 8.09 (d, 1 H, J = 8 Hz, H-10), 8.13 (s, 1 H, H-6).

Dimethyl 7-(Benzylidenamino)pyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (10):
A mixture of pyridazine (**9**; 0.20 g, 2.5 mmol), dimethyl maleate (**2**; 0.72 g,. 5 mmol), Me_4NBr (0.077 g, 0.5 mmol), and powdered KOH (0.112 g, 2 mmol) in $CHCl_3$ (30 mL) was stirred vigorously at 13–15 °C under Ar for 1.5 h and then additional powdered KOH (0.55 g, 8 mmol) in a small portion was added for 4.5 h. The precipitate was separated by filtration, washed with $CHCl_3$ (2 × 5mL), and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel using 33 % EtOAc/hexane as eluent. A product fraction was concentrated in vacuo to 2 mL (warning: when evaporating to dryness the product was easily oxidized) and diluted with benzene (15 mL). To the solution was added benzylamine (**4**; 0.32 g, 3.0 mmol) and the mixture was refluxed under Ar for 2 h. Precipitated amine hydrochloride was filtered and the precipitate was washed with benzene (2 × 5 mL). To the filtrate was added activated MnO_2 (2 g, 23 mmol) and the suspension was stirred vigorously at 60 °C for 1 h. The precipitate was separated by filtration, washed with $CHCl_3$ until the washings were colorless and the filtrate was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (15 mL) and the solution was shaken with conc. HCl (0.1 mL), followed by H_2O (15 mL). The layers were separated and the organic layer was washed with 5 % aq Na_2CO_3 (10 mL), followed by H_2O (10 mL), and dried (Na_2SO_4). The solvent was evaporated on a rotary evaporator in vacuo and the residue was crystallized from Et_2O; bright yellow needles; yield: 0.254 g (30 %); mp 148–150 °C.

$C_{18}H_{15}N_3O_4$	calc.	C 64.09	H 4.48	N 12.46
(337.3)	found	63.97	4.56	12.58

IR ($CHCl_3$): ν = 1740, 1710 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 274 (4.47), 363 nm (4.43).

^1H NMR ($CDCl_3$/HMDS): δ = 3.90 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.89 (dd, 1 H, J = 9.5, 4.5 Hz, H-3), 7.43–7.49 (m, 3 H, 3 $H_{m,p\text{-arom}}$), 7.92–8.02 (m, 2 $H_{o\text{-arom}}$), 8.34 (dd, 1 H, J = 4.5, 1.7 Hz, H-4).

Dimethyl 7-Aminopyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylate (11):
Compound **10** (0.254 g, 0.75 mmol) was dissolved in $CHCl_3$ (1 mL) and chromatographed through a silica gel column by elution with hexane containing increasing amount of EtOAc (from 15 % to 30 %). An orange fraction was collected and evaporated in vacuo and the residue was crystallized from Et_2O; orange needles; yield: 0.18 g (96 %); mp 134.5–135.5 °C.

$C_{11}H_{11}N_3O_4$	calc.	C 53.01	H 4.45	N 16.86
(249.2)	found	53.09	4.44	16.76

IR ($CHCl_3$): ν = 3490, 3380, 1730, 1690 cm^{-1}.

UV (EtOH): λ_{max} (log ε) = 210 (4.50), 262 (4.20), 290 (4.02), 438 nm (3.91).

^1H NMR ($CDCl_3$/HMDS): δ = 3.95 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.61 (br s, 2 H, NH_2), 6.57 (dd, 1 H, J = 9.6, 4.4 Hz, H-3), 8.01 (dd, 1 H, J = 4.4, 1.6 Hz, H-4), 8.15 (dd, 1 H, J = 9.6, 1.6 Hz, H-2).

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