Synthesis of 6-Phenyl-Atevirdine

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The synthesis of 6-phenyl-atevirdine (**17**), a lipophilic derivative of the potent HIV-1 reverse transcriptase inhibitor atevirdine (**1**), is described. The title compound was prepared from dithioacetale **2** *via* keteneaminal **4** and the nitropyridine derivative **10**. Unexpectedly, no anti HIV activity was observed for the novel atevirdine derivative **17**. The key intermediates **6, 8** and **10** could also be prepared from keteneaminal **18** *via* chloropyridines **22-24**.

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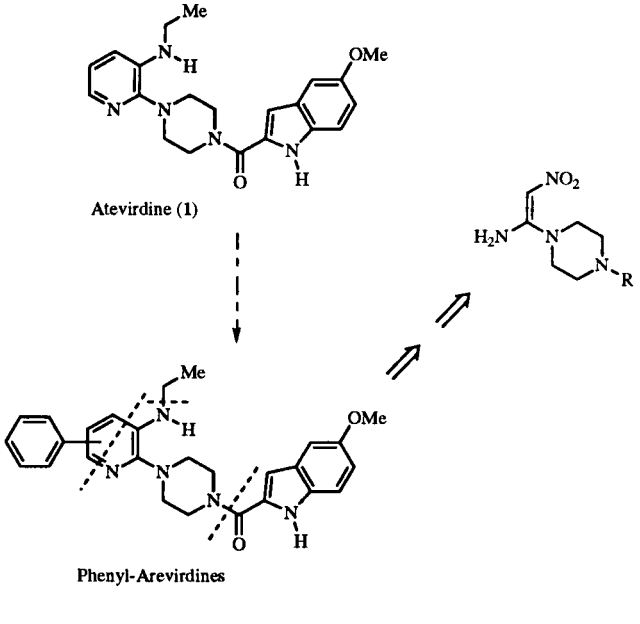
Certain bis(heteroaryl)piperazines are potent inhibitors of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. Extensive preclinical evaluations of several of these compounds led to the selection of 1-[(5-methoxy-indol- 2-yl)carbonyl]-4-[3-(ethylamino)-2-pyridyl]piperazine (atevirdine, **1**) for further clinical evaluation [1,2]. In the course of synthesis of functional pyridines as potential drugs [3-5], we devised a synthesis of more lipophilic atevirdine derivatives which could pass the blood-liquor-barrier [6]. For this reason, the pyridine ring in atevirdine was substituted with an additional lipophilic phenyl moiety.

A short retrosynthetic view (see Scheme 1) shows, that a primary-tertiary nitroketeneaminal should serve as key intermediate. A cyclocondensation of this keteneaminal with phenyl substituted C_3-building blocks was expected to provide phenyl substituted pyridine derivatives, which would then be transformed into atevirdine derivatives.

Scheme 1



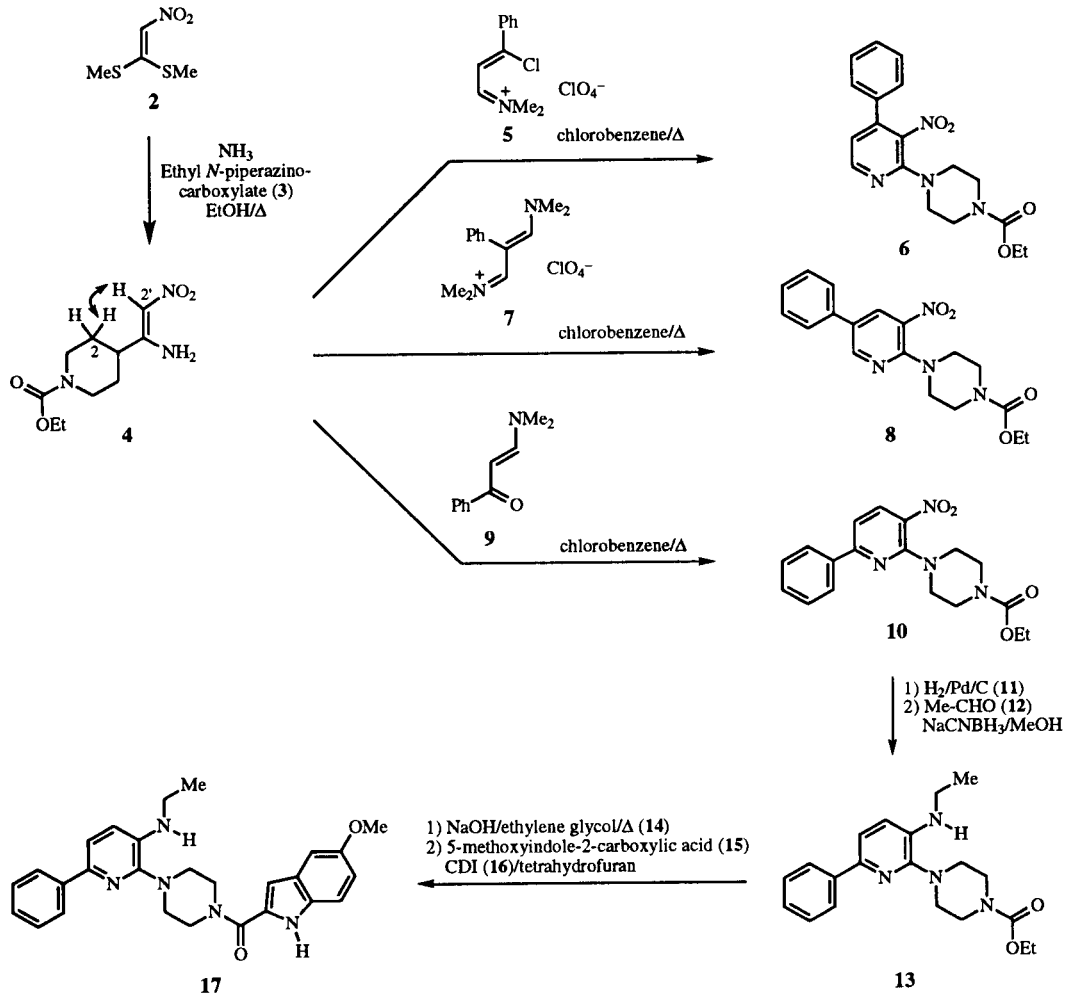
The preparation of intermediates **6, 8** and **10** started with the aminolysis of dithioacetale **2** with ammonia and ethyl *N*-piperazinocarboxylate (**3**) (Scheme 2). For the resulting keteneaminal **4**, ^1H NOE measurements revealed the *E*-configuration. The synthesis of 4-phenyl substituted pyridine **6** by cyclocondensation of keteneaminal **4** with phenylpropiolic aldehyde failed. In an alternative route we used the chloropropeneiminium salt **5** as a C_3-building block, which was easily obtained from acetophenone and dimethylformamide/phosphoryl chloride/perchloric acid [7]. Refluxing **5** and keteneaminal **4** in chlorobenzene gave the desired pyridine **6** in good yields. The position of the phenyl ring at C-4 in **6** was determined from the ^1H-coupling constant (J = 4.5 Hz) observed for H-5 and H-6 in the ^1H nmr. As a by-product, the isomeric 6-phenyl-pyridine **10** was obtained in low yields (*ca.* 5%). The preparation of the 5-phenyl substituted pyridine **8** was accomplished by refluxing **4** and the trimethinium salt **7** in chlorobenzene yielding the target compound in only low yields (*ca.* 20%) [8].

Treatment of **4** with the enaminone **9** afforded the 6-phenyl substituted pyridine **10** in 70% yield after prolonged reaction time (9 days).

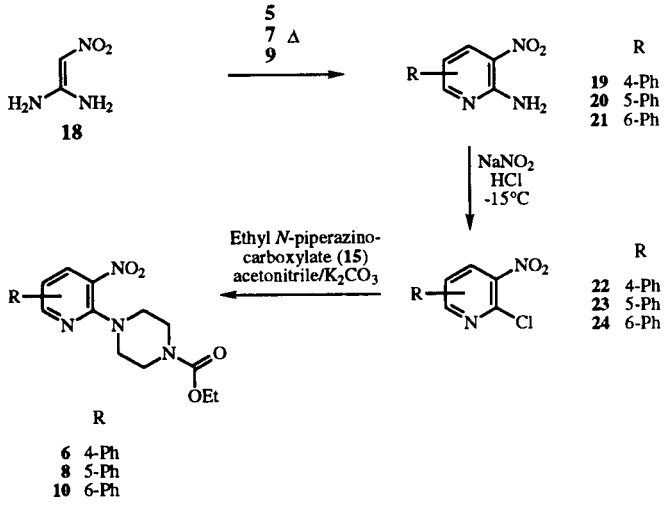
For the preparation of atevirdine derivative **17** (see Scheme 2), the nitro group in **10** had to be reduced by hydrogenation. The resulting amine **11** was then treated with acetaldehyde (**12**)/sodium cyanoborohydride to yield **13** with the desired ethylamino substituent. After removal of the ethyl ester group in **13** with sodium hydroxide in refluxing ethylene glycol, the arylpiperazine **14** was coupled with 5-methoxyindole-2-carboxylic acid (**15**) utilizing carbonyldiimidazole **16**.

The thus obtained atevirdine derivative **17** has been evaluated for *in-vitro* anti HIV activity in the Anti-Aids Drug Discovery Program of the NHI (NCI). Since the 6-phenyl-atevirdine **17** was judged to be "Inactive", the pyridines **6** and **8** have so far not been transformed into the 4-phenyl and 5-phenyl-atevirdine derivatives. Finally, it should be mentioned that the pyridine derivatives **6, 8** and **10** are available by an alternative route (see Scheme 3), *i.e.* by cyclocondensation of 2-nitroethene-1,1-diamine (**18**) with C_3-building blocks **5, 7** and **9** to the 3-nitropyridin-2-

Scheme 2



Scheme 3



amines **19**, **20** and **21**. The latter compounds are transformed to the chloropyridines **22**, **23** and **24** by treatment with sodium nitrite in concentrated hydrochloric acid at -15°. The final aminolysis of the chloropyridines **22-24** with ethyl *N*-piperazinocarboxylate (**15**) gives the nitropyridine-piperazines **6**, **8** and **10** in fairly good yields.

EXPERIMENTAL

All melting points were determined using a Büchi-530 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer-1740 spectrometer. The ^{1}H nmr spectra were obtained with a Bruker-BZH-360/52 instrument with tetramethylsilane as the internal standard. The mass spectra were recorded on a Finnigan-4500 instrument at 70eV.

Ethyl (*E*)-4-(1-Amino-2-nitroethene-1-yl)-1-piperazinocarboxylate (**4**).

A solution of **2** (1.65 9, 0.01 mole) and ethyl *N*-piperazinocarboxylate (**3**) (1.58 g, 0.01 mole) in ethanol (20 ml) was heated for 3.5 hours at reflux during which time gaseous ammonia was bubbled through the solution. The organic solvent was evaporated *in vacuo* and the residue was crystallized from methanol to yield 1.83 g (75%), mp 137-138°; ir (potassium bromide): 3277,

3168 and 3133 (NH_2), 2984, 2932 and 2908 (CH), 1677 (CO), 1579 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.42-3.50 (m, 4H, 3-H and 5-H), 3.59-3.67 (m, 4H, 2-H and 6-H), 4.18 (q, 2H, OCH_2CH_3, J = 7 Hz), 6.62 (s, 1H, 2-H, ethene), 8.11 ppm (br s, 2H, NH_2, deuterium oxide-exchangeable); ms: m/z 244 (M^+), 198 ($M^+ - NO_2$).

Anal. Calcd. for $C_9H_{16}N_4O_4$ C, 44.26; H, 6.60; N, 22.94. Found: C, 44.29; H, 6.66; N, 23.01.

Ethyl 4-(3-Nitro-4-phenyl-2-pyridyl)-1-piperazinocarboxylate (**6**).

Method A.

A solution of **4** (244 mg, 1.00 mmole) and **5** (294 mg, 1.00 mmole) in chlorobenzene (10 ml) was heated at reflux for 2 hours. The organic solvent was evaporated *in vacuo* and the residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 8:2, v/v) to yield 192 mg (54%), mp 73-75°; ir (chloroform): 3014, 2926 and 2865 (CH), 1690 (CO), 1538 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.31-3.41 (m, 4H, 3-H and 5-H), 3.55-3.63 (m, 4H, 2-H and 6-H), 4.17 (q, 2H, OCH_2CH_3, J = 7 Hz), 6.87 (d, 1 H, 5-H, pyridine, J = 5Hz), 7.29-7.36 (m, 2H, aromatic protons), 7.40-7.46 (m, 3H, aromatic protons), 8.34 ppm (d, 1 H, 6-H, pyridine, J = 5 Hz); ms: m/z 356 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.67; N, 15.72. Found: C, 60.49; H, 5.66; N, 15.69.

Method B.

To a cooled (0°) mixture of **22** (120 mg, 0.51 mmole) and potassium carbonate (81 mg, 0.59 mmole) in acetonitrile (10 ml) was added slowly ethyl *N*-piperazinocarboxylate (**15**) (81 mg, 0.59 mmole). The reaction mixture was stirred overnight at room temperature, treated with water (5 ml) and was extracted with methylene chloride. The organic layer was dried (sodium sulphate), evaporated *in vacuo* and the residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 7:3, v/v) yielding 82 mg (45%).

Ethyl 4-(3-Nitro-5-phenyl-2-pyridyl)-1-piperazinocarboxylate (**8**).

Method A.

A solution of **4** (250 mg, 1.02 mmoles) and **7** (309 mg, 1.02 mmoles) in chlorobenzene (20 ml) was heated at reflux for 72 hours. After being cooled to room temperature, water was added and the mixture was extracted with ether. The organic layer was dried (sodium sulphate) and evaporated *in vacuo*. The residual oil was separated by mplc on silica gel (toluene:acetone 95:5, v/v) yielding 73 mg (20%), mp 100-102°; ir (potassium bromide): 3012, 2958, 2925 and 2866 (CH), 1685 (CO), 1551 cm^{-1} (NO_2); ^1H nmr (chloroform): δ 1.29 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.45-3.52 (m, 4H, 3-H and 5-H), 3.61-3.68 (m, 4H, 2-H and 6-H), 4.19 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.35-7.57 (m, 5H, aromatic protons), 8.37 and 8.61 ppm (2d, each 2H, 4-H and 6-H, pyridine, J = 2 Hz); ms: m/z 356 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.67; N, 15.72. Found: C, 60.70; H, 5.66; N, 15.69.

Method B.

To a cooled (0°) mixture of **23** (188 mg, 0.80 mmole) and potassium carbonate (138 mg, 1.00 mmole) in acetonitrile (10 ml) was added slowly ethyl *N*-piperazinocarboxylate (**15**) (127 mg, 0.80 mmole). The mixture was stirred at room temperature for 5 hours, treated with water and extracted with methylene chloride. The organic solvent was separated, dried (sodium sulphate) and evaporated *in vacuo* to give 271 mg (95%).

Ethyl 4-(2-Nitro-6-phenyl-2-pyridyl)-1-piperazinocarboxylate (**10**).

Method A.

A solution of **4** (244 mg, 1.00 mmole) and **9** (175 mg, 1.00 mmole) in chlorobenzene (10 ml) was heated at reflux for 9 days. The organic solvent was evaporated *in vacuo* and the residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 9:1, v/v) to yield 250 mg (70%), mp 70-72°; ir (chloroform): 3020, 2929 and 2853 (CH), 1688 (CO), 1594, 1576, 1571, 1333 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.50-3.60 (m, 4H, 3-H and 5-H), 3.62-3.72 (m, 4H, 2-H and 6-H), 4.19 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.27 (d, 1H, 5-H, pyridine, J = 8.5 Hz), 7.46-7.52 (m, 3H, aromatic protons), 7.98-8.05 (m, 2H, aromatic protons), 8.29 ppm (d, 1 H, 4-H, pyridine, J = 8.5 Hz); ms: m/z 356 (M^+).

Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.67; N, 15.72. Found: C, 60.72; H, 5.65; N, 15.75.

Method B.

A mixture of ethyl *N*-piperazinocarboxylate (**15**) (633 mg, 4.00 mmoles) and potassium carbonate (560 mg) in acetonitrile (20 ml) was cooled at 0°. To the mixture was added **24** (938 mg, 4.00 mmoles) and stirred at room temperature for 48 hours. Water and chloroform were added and the organic layer was separated, dried (sodium sulphate) and evaporated *in vacuo* to give 1.35 g (95%).

Ethyl 4-(3-Amino-6-phenyl-2-pyridyl)-1-piperazinocarboxylate (**11**).

To a solution of **10** (323 mg, 0.91 mmole) in ethyl acetate (130 ml) was added 97 mg of palladium (10% on carbon) and the mixture was hydrogenated at room temperature (3.6 bar) for 6 hours. The mixture was filtered through Celite and the solvent was evaporated *in vacuo*. The residue was crystallized from ethanol/water to give 260 mg (87%), mp 171-173°; ir (chloroform): 3454 and 3358 (NH_2), 3031 and 3012 (CH), 1685 (CO), 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, OCH_2CH_3, J = 7 Hz), 3.22 (br s, 6H, 3-H, 5-H and NH_2), 3.68 (br s, 4H, 2-H and 6-H), 4.16 (q, 2H, OCH_2CH_3, J = 7 Hz), 7.22 and 7.35 (2d, each, 1H, 5-H and 4-H, pyridine, J = 8 Hz), 7.25-7.44 (m, 3H, aromatic protons), 7.88-7.95 ppm (m, 2H, aromatic protons); ms: m/z 326 (M^+).

Anal. Calcd. for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found: C, 66.16; H, 6.84; N, 17.22.

Ethyl 4-(3-Ethylamino-6-phenyl-2-pyridyl)-1-piperazinocarboxylate (**13**).

A solution of **11** (1.14 g, 3.50 mmoles) and acetaldehyde (**12**) (440 mg, 0.01 mole) in methanol (20 ml) was cooled (0°) and treated with sodium cyanoborohydride (220 mg, 3.50 mmoles). The mixture was stirred at room temperature for 2 days. Water and methylene chloride were added, the organic solvent was separated and dried (sodium sulphate). After evaporation of the solvent *in vacuo*, the residue was purified by mplc (cyclohexane:ethyl acetate 9:1, v/v) yielding 955 mg (77%), mp 75-76°; ir (chloroform): 3375 (NH), 3066, 3033 and 3012 (CH), 1685 (CO), 1584 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 and 1.32 (2t, each, 3H, OCH_2CH_3 and NCH_2CH_3, J = 7 Hz), 3.10-3.24 (m, 6H, 3-H, 5-H and

NCH_2CH_3), 3.60-3.69 (m, 4H, 2-H and 6-H), 4.18 (q, 3H, OCH_2CH_3, J = 7 Hz and NH, deuterium oxide-exchangeable), 6.88 and 7.41 (2d, each 1H, 4-H and 5-H, pyridine, J = 8 Hz), 7.22 and 7.45 (m, 3H, aromatic protons), 7.91-7.98 ppm (m, 2H, aromatic protons); ms: m/z 354 (M^+).

Anal. Calcd. for $C_{20}H_{26}N_4O_2$: C, 67.77; H, 7.39; N, 15.81. Found: C, 67.83; H, 7.36; N, 15.84.

1-(3-Ethylamino-6-phenyl-2-pyridyl)piperazine (**14**).

A mixture of **13** (195 mg, 0.55 mole) and sodium hydroxide (2 ml of a saturated solution) in ethylene glycol (10 ml) was heated at 150°. After being cooled to room temperature, a colorless solid was filtered and dried to yield 135 mg (87%), mp 77-79; ir (potassium bromide): 3323 and 3268 (NH), 3062, 3035, 2965, 2930 and 2846 (CH), 1581 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H, NCH_2CH_3 J = 7 Hz), 3.03-3.09 (m, 4H, 3-H and 5-H), 3.12-3.22 (m, 6H, 2-H, 6-H and NCH_2CH_3), 4.24 (br t, 1H, $NHCH_2CH_3$, deuterium oxide-exchangeable, J = 5 Hz), 6.88 and 7.41 (2d, each, 1 H, 4-H and 5-H, pyridine, J = 8 Hz), 7.24-7.30 (m, 1H, aromatic proton), 7.37-7.42 (m, 2H, aromatic protons), 7.94-7.98 ppm (m, 2H, aromatic protons); ms: m/z 282 (M^+).

1-[(5-Methoxyindole-2-yl)carbonyl]-4-[3-(ethylamino)-6-phenyl-2-pyridyl]piperazine (**17**), (6-Phenyl-Atevirdine).

To a cooled (0°) solution of 5-methoxyindole-2-carboxylic acid (**15**) (19 mg, 0.10 mmole) and *N,N'*-carbonyldiimidazole (**16**) (16 mg, 0.10 mmole) in tetrahydrofuran (5 ml) the piperazine **14** (28 mg, 0.10 mmole) was added. The reaction mixture was stirred at room temperature for 20 hours, the organic solvent was evaporated *in vacuo* and the residue was purified by mplc (cyclohexane:ethyl acetate 6:4, v/v) yielding 28 mg (62%), mp 209-211°; ir (potassium bromide): 3400 (NH), 3061, 3033, 2966, 2926 and 2830 (CH), 1607 (CO), 1528 cm^{-1}; ^1H nmr (chloroform): δ 1.35 (t, 3H, $NHCH_2CH_3$, J = 7 Hz), 3.22 (dq, 2H, $NHCH_2CH_3$, J_1 = 7 Hz, J_2 = 5.5 Hz), 3.29-3.35 (m, 4H, 3-H and 5-H), 3.85 (s, 3H, OMe), 4.06-4.19 (m, 4H, 2-H and 6-H), 4.24 (br t, 1H, NH, deuterium oxide-exchangeable, J = 5.5 Hz), 6.78 (dd, 1 H, 3-H, indole, J_1 = 2.5 Hz, J_2 = 1 Hz), 6.93 and 7.43 (2d, each, 1H, 4-H and 5-H, pyridine, J = 8 Hz), 6.96 (dd, 1H, 6-H, indole, J_1 = 8.5 Hz, J_2 = 2.5 Hz), 7.08 (d, 1H, 4-H, indole, J = 2.5 Hz), 7.23-7.41 (m, 4H, 7-H, indole and aromatic protons), 7.92-7.98 (m, 2H, aromatic protons), 9.18 ppm (br s, 1H, NH, indole, deuterium oxide-exchangeable); ms: m/z 455 (M^+).

Anal. Calcd. for $C_{27}H_{28}N_5O_2$: C, 71.34; H, 6.21; N, 15.41. Found: C, 71.35; H, 6.18; N, 15.45.

3-Nitro-4-phenylpyridin-2-amine (**19**).

A solution of **5** (1.00 g, 3.40 mmoles) and **18** (315 mg, 3.40 mmoles) in chlorobenzene (30 ml) was heated at reflux for 8 hours. The organic solvent was evaporated *in vacuo* and the residue was purified by mplc on silica gel (cyclohexane:ethyl acetate 8:2, v/v) yielding 315 mg (43%), mp 129-130°; ir (potassium bromide): 3492, 3275 and 3119 (NH_2), 1635, 1459, 1325, 1314 cm^{-1}; ^1H nmr (chloroform): δ 5.90 (br s, 2H, NH_2, deuterium oxide-exchangeable), 6.68 (d, 1H, 5-H, J = 5 Hz), 7.28-7.34 (m, 2H, aromatic protons), 7.40-7.47 (m, 3H, aromatic protons), 8.24 ppm (d, 1H, 6-H, J = 5 Hz); ms: m/z 215 (M^+).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.52. Found: C, 61.38; H, 4.23; N, 19.49.

3-Nitro-5-phenylpyridin-2-amine (**20**).

A solution of **18** (510 mg, 4.95 mmoles), **7** (1.50 g, 4.95 mmoles) and sodium (114 mg, 4.95 mmoles) in 1-butanol (70 ml) was heated at reflux for 7 hours. A brown solid was filtered and crystallized from ethanol to give 522 mg (49%), mp 190-191°; ir (potassium bromide): 3467, 3289 and 3139 (NH_2), 1657, 1561 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.35-7.41 (m, 1 H, aromatic proton), 7.45-7.51 (m, 2H, aromatic protons), 7.69-7.75 (m, 2H, aromatic protons), 8.01 (br s, 2H, NH_2, deuterium oxide-exchangeable), 8.58 and 8.79 ppm (2d, each, 1H, 4-H and 6-H, pyridine, J = 2.5 Hz); ms: m/z 215 (M^+).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.52. Found: C, 61.34; H, 4.18; N, 19.55.

2-Chloro-3-nitro-4-phenylpyridine (**22**).

A cooled mixture (-15°) of **19** (43 mg, 0.20 mmole) and hydrochloric acid (10 ml) was treated slowly with sodium nitrite (276 mg, 4.00 mmoles). The reaction mixture was stirred at room temperature for 5 hours and was then extracted with ether. The organic solvent was washed with water, dried (sodium sulphate) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane:ethyl acetate 7:3, v/v) to yield 24 mg (51%), mp 65-67°; ir (chloroform): 3064, 3022 and 3009 (CH), 1588, 1544 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): δ 7.38 (d, 1H, 5-H, J = 5 Hz), 7.35-7.42 and 7.44-7.53 (2m, 5H, aromatic protons), 8.55 ppm (d, 1 H, 6-H, J = 5 Hz); ms: m/z 236/234 (M^+).

Anal. Calcd. for $C_{11}H_7ClN_2O_2$: C, 56,30; H, 3.01; N, 11.94. Found: C, 56.34; H, 3.03; N, 11.91.

2-Chloro-3-nitro-5-phenylpyridine (**23**).

A cooled (-15°) solution of **20** (2.15 g, 0.01 mole) in hydrochloric acid (60 ml) was treated slowly with sodium nitrite (27.6 g, 0.40 mole). After 5 hours the mixture was carefully diluted with water. A precipitating pale yellow solid was filtered and washed with water to give 1.31 g (56%), mp 97-99°; ir (potassium bromide): 3064 (CH), 1582, 1553, 1527 (NO_2), 1066 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.50-7.61 (m, 3H, aromatic protons), 7.84-7.89 (m, 2H, aromatic protons), 8.86 and 9.08 ppm (2d, each, 4-H and 6-H, pyridine, J = 2 Hz); ms: m/z 236/234 (M^+).

Anal. Calcd. for $C_{11}H_7ClN_2O_2$: C, 56,30; H, 3.01; N, 11.94. Found: C, 56.29; H, 3.02; N, 11.99.

2-Chloro-3-nitro-6-phenylpyridine (**24**).

A cooled (-15°) mixture of **21** (430 mg, 2.00 mmoles) and hydrochloric acid (15 ml) was treated slowly with sodium nitrite (2.76 g, 0.04 mole). The mixture was stirred at room temperature overnight during a yellow solid precipitated. After filtration, washing with water and drying the solid was purified by column chromatography on silica gel (chloroform:methanol 98:2, v/v) to yield 211 mg (45%), mp 112-113°; ir (potassium bromide): 3081 (CH), 1577, 1567, 1526 cm^{-1} (NO_2); ^1H nmr (chloroform): δ 7.51-7.55 (m, 3H, aromatic protons), 7.82 (d, 1H, 5-H, pyridine, J = 8.5 Hz), 8.01-8.05 (m, 2H, aromatic protons), 8.32 ppm (d, 1H, 4-H, pyridine, J = 8.5 Hz); ms: m/z 236/234 (M^+).

Anal. Calcd. for $C_{11}H_7ClN_2O_2$: C, 56,30; H, 3.01; N, 11.94. Found: C, 56.26; H, 3.02; N, 11.96.

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