Preparation of 6-Azaoxindole (6-Azaindol-2(3*H*)-one) and Substituted Derivatives

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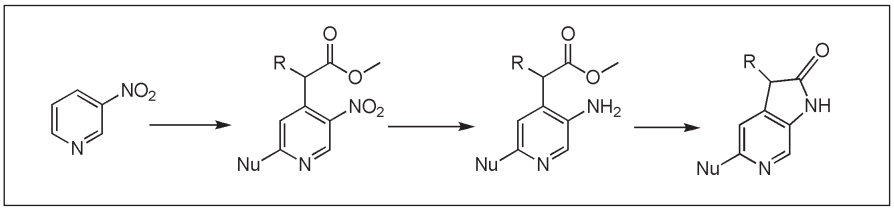

A general synthesis of 6-azaoxindoles, substituted in the 3- and 5-position, has been developed starting from 4-methoxycarbomethyl-3-nitropyridine, via hydrogenation of the nitro group and cyclisation of the resulting 3-amino-4-methoxycarbomethyl-pyridine.

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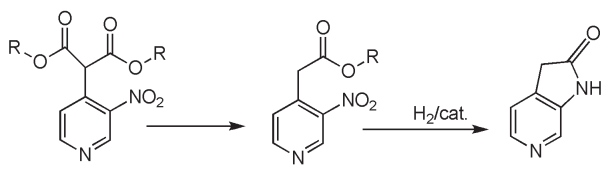
Introduction.

We have reported the synthesis of 4-methoxycarbomethyl-3-nitropyridine (**1a**) by a vicarious nucleophilic substitution (VNS) of the readily available 3-nitropyridine. Furthermore, we showed that the VNS reaction was also possible with potassium 5-nitropyridine-2-sulfonate [1]. The products from the VNS reactions and their further substitution products have the "ortho" configuration of the nitro and ester groups which makes a ring closure possible after reduction of the nitro group to an amino group.

The products from a ring closure reaction would be 6-azaoxindoles (6-azaindol-2(3H)-ones, **3**). The azaindole ring system is part of several pharmaceutical and natural products and several synthetic methods have been reported for azaindoles, including 6-azaindoles [2]. Azaoxindoles have been less thoroughly investigated. A few patents for pharmaceutical products containing the azaoxindoles have appeared [3] and syntheses for 6-azaoxindole itself have been reported [3,4]. These started with 4-chloro-3-nitropyridine which was reacted with diethyl [3,4a] or dibenzyl [4b] malonate. The products were hydrogenated and the diethyl esters decarboxylated either before [3] or after [4a] the cyclisation to azaoxindole. With the dibenzyl ester, the decarboxylation took place during the hydrogenation/ cyclisation reaction and 6-azaoxindole was formed in a one-pot reaction (76% yield). Although the yields in the cyclisation reaction were satisfactory, the yields in the first steps, especially the reaction of 4-chloro-3-nitropyridine with the malonate diesters were low [3]. Furthermore, substituted 6-azaoxindoles are not easily available by this method.



R = Et [3,4a], Bn [4b]

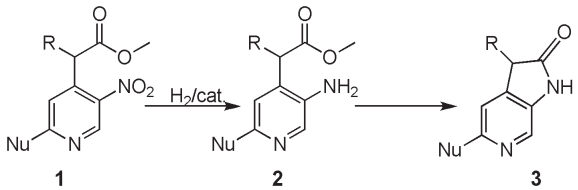
The new high yield method for the formation of **1a** [1] makes this an attractive compound for the synthesis of 6-azaoxindole. It might also be possible to prepare substituted derivatives of **1** and thus obtain a general synthesis of 6-azaoxindoles substituted in the 3- and 5-positions by reduction of **1** to the 3-aminopyridine, compound **2**, followed by cyclisation to the 6-azaoxindoles (**3**).

Results and Discussion.

Preparation of Compounds **1b – 1e**.

The possibility of substitution of **1a** in the side chain was explored with a few alkylating agents, methyl and ethyl iodides and benzyl bromide. The monoalkylation reaction in MeONa/MeOH gave acceptable yields, 42%, 53% and 41% respectively. However, attempts at dialkylation failed, both in the reaction of **1b** with ethyl iodide and of **1c** with methyl iodide. Attempts at alkylations with 1-bromo-3-chloropropane and 1-bromo-4-chlorobutane also failed. With these compounds, the bromide ion apparently was not a good enough leaving group to facilitate the reactions. Neither were we able to alkylate the 2-methoxy

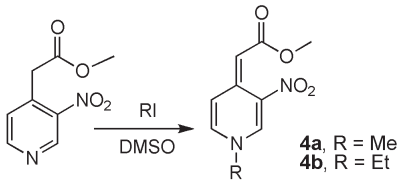
Scheme 1



	R	Nu
1a	H	H
1b	Me	H
1c	Et	H
1d	Bn	H
1e	H	OMe

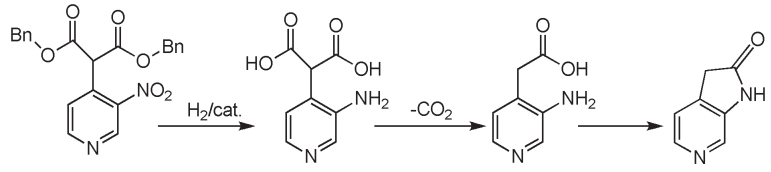
compound **1e** by the methods above, presumably because the methoxy group para to the nitro group, mitigates its electron withdrawing effect.

An unexpected reaction took place during these experiments. In an attempt to increase the yield in the preparation of **1b**, **1a** was reacted with methyl iodide in DMSO/NaH. Instead of **1b** a deep red compound was isolated in 80% yield, which by MS and NMR spectroscopy was shown to be the N-methylated 4-pyridone **4a**. An even higher yield of this, 93%, was obtained by reaction of **1a** with dimethyl sulfate and NaH in THF. A small amount of **4a** was also found in the preparation of **1a** in MeOH, showing the fine balance between C- and N-attack in this reaction. In the reaction of **1a** with ethyl iodide in MeONa/MeOH, a 2% yield of the analogous N-ethylated 4-pyridone **4b** was isolated.



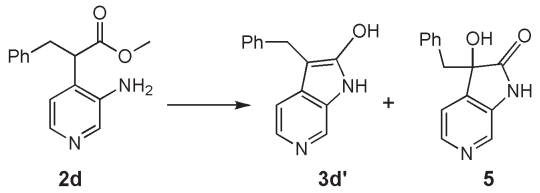
Formation of 6-Azaoxindoles.

The cyclisation of **2** might take place under different conditions. The product from catalytic hydrogenation of 4-bis(benzyloxycarbo)methyl-3-nitropyridine gave 6-azaoxindole in 76% yield upon heating in ethanol solution [4]. A reasonable result from the catalytic hydrogenation would be the formation of 4-carboxymethyl-3-nitropyridine from reductive cleavage of the benzyl esters followed by decarboxylation:



In an attempt to apply this methodology, we hydrogenated the benzyl ester of 4-(carboxymethyl)-3-nitropyridine. The free acid, 4-(carboxymethyl)-3-aminopyridine was formed in 65% yield. However, reaction of this in refluxing ethanol as described for the product from the hydrogenation of the bisbenzyl ester, gave 4-methyl-3-aminopyridine as the only product (close to 100% by NMR). Apparently, the reaction of the bisbenzyl ester did not proceed by the route above.

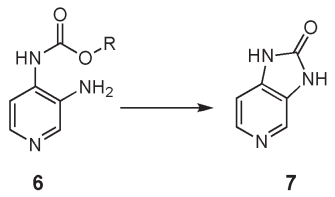
In an attempt to perform the cyclisation under basic conditions, **2a** was reacted with 1.5 mol eq. NaOEt in ethanol. The conversion to 6-azaoxindole was complete after 24 h at room temperature (^{1}H NMR). Thus, the cyclisation reaction went smoothly under these conditions, but the isolation of the product was difficult. Although NMR indicated **3a** to be the only product it was only possible to isolate a low yield of **3a**. When 4-(benzyl-methoxycarbomethyl)-3-aminopyridine (**2d**) was reacted under basic conditions, only one product was obtained in 61% yield. From MS, NMR and IR spectroscopy this was 3-benzyl-3-hydroxy-6-azaoxindole (**5**):



In the formation of **5** there must have been an oxidation stage, most likely an autoxidation of the "enol form" **3d'** under basic conditions. The easy autoxidation of an isomer of **3d**, 3-benzyl-4-azaoxindole has been reported [5].

Reaction under acidic conditions also resulted in complete conversion of **2a** to 6-azaoxindole (**3a**) as indicated by ^{1}H NMR spectroscopy. In contrast to the product from the reaction under basic conditions, **3a** was readily isolated as its HCl salt. This methodology was then applied to compounds **2b** and **2d**. In both cases satisfactory yields of the substituted 6-azaoxindoles **3b** and **3d** as the HCl salts were obtained (Table 1).

Late in this investigation, Fiksdahl and Holt [6] found, in a different project, that methyl 3-aminopyridin-4-yl carbamate (**6**) readily cyclised at 50 °C to 1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (**7**) with HBF_4 as catalyst.



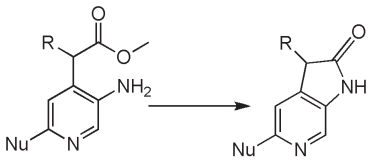
This cyclisation reaction had been performed earlier under more severe conditions, 150 °C in diglyme for 24 h [7]. We therefore tried the HBF_4 protocol with **2a** as substrate. This worked well: in aqueous solution with 3.5 mol

eq. HBF_4, the cyclisation reaction was complete after 0.5 h at reflux temperature. The work up was easy and a 63% yield of the free base **3a** was isolated. We then tried this method for the other aminopyridines **2b** – **2e** the yields were lower then for the cyclisations with HCl but the reported yields are from the isolation of the free base, not the acid salts. The results may therefore not be directly comparable.

We were not able to alkylate the 2-methoxy compound **1e** in the side chain. We therefore alkylated the 6-azaoxindole **3e** with methyl iodide. The only product from that reaction was 3,3-dimethyl-5-methoxy-6-azaoxindole **3f**. Even if only 0.5 mol eq. of MeI was reacted, the dimethylated oxindole was the product together with an equivalent amount of unreacted **3e**.

Table 1

Formation of 6-Azaoxindoles from 3-Amino-4-methoxycarbomethylpyridines



2 **3**

R	Nu	Yields/% *Conditions* HCl/H_2O/$(C_2H_5)_2O$[a]	HBF_4/H_2O[b]
H	H (**3a**)	98	63
Me	H (**3b**)	90	13
Et	H (**3c**)	-	98
Bn	H (**3d**)	61	51
H	MeO (**3e**)	-	98
Me_2	MeO (**3f**)[c]		30

[a] Yields of product isolated as HCl salt; [b] Yields of product isolated as free base; [c] Yield from alkylation of **3e**.

From Table 1 it can be seen that a general method for the synthesis of 6-azaoxindoles substituted in the 3- and 5-positions has been elaborated, starting from the readily available 3-nitropyridine via 4-methoxycarbomethyl-3-nitropyridine (**1a**). This may open a new route to a series of compounds with the potential for biological activity.

EXPERIMENTAL

NMR spectra were recorded on Bruker Avance DPX 300, DPX 400 or DRX 600 instruments with chemical shifts referenced to the residual ^1H or ^{13}C resonances of the deuteriomethanol or deuteriodimethylsulfoxide solvent employed. Coupling constants are given in Hz. IR spectra were recorded on a Thermo Nicolet FT-IR Nexus spectrometer. EI-MS spectra were obtained on a Finnigan MAT 95XL spectrometer. Melting points are uncorrected. Elemental analyses were determined by the Laboratory of Organic Elemental Analysis, Institute of Chemical Technology, Prague, Czech Republic. Solvents were purified by standard methods [8]. Silica gel SDS 60A, 43-60 mesh was used for flash column chromatography.

4-(Benzyloxycarbomethyl)-3-nitropyridine.

3-Nitropyridine (1.0 g, 8.1 mmol) and benzyl chloroacetate (2.0 ml, 13.2 mmol) were dissolved in dry DMF (9 ml) and during 5 minutes added dropwise to a solution of potassium *t*-butoxide (3.6 g, 32 mmol) in dry DMF (36 ml) cooled in an ice-water bath. The cooling bath was removed and the reaction mixture stirred for 35 minutes before it was quenched by addition of an excess of aqueous ammonium chloride (3 *M*). The aqueous phase was then extracted with diethyl ether (4 x 50 ml). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give the crude product as a red oil, 2.50 g. Purification by flash chromatography (ethyl acetate:petroleum ether (80-100 °C) 1:1) gave the pure product as a light yellow solid, 1.64 g (75%). mp 64.5-65.5 °C; IR (neat) max/cm^{-1}: 1727 (s), 1609 (s), 1556 (s), 1455 (m), 1381 (s), 1350 (s), 1303 (s), 1226 (s); ^1H NMR (400 MHz, d_6-DMSO): 9.25 (1H, s, H-2), 8.86 (1H, d, *J* = 4.94 Hz, H-6), 7.68 (1H, d, *J* = 4.94 Hz, H-5), 7.42-7.30 (5H, m, Ph), 5.14 (2H, s, OC**H**$_2$), 4.25 (2H, s, C**H**$_2$(CO)); ^{13}C NMR (100 MHz, d_6-DMSO): 168.9. 154.1, 145.7, 145.0, 138.8, 135.7, 128.5, 128.2, 128.0, 127.9, 66.3, 36.3; m/z (EI) 273.08794 (M+1, $C_{14}H_{13}N_2O_4$ requires 273.08753), 273 (M+1, 0.4), 166 (64), 136 (65), 108 (30), 91 (100), 86 (30), 84 (46), 65 (13).

Alkylation Reactions, General Method.

4-(Methoxycarbomethyl)-3-nitropyridine [1] (**1a**) (5.1 mmol) and alkyl iodide (5.6 mmol) in dry MeOH or EtOH (15 ml) were added dropwise to a solution of sodium methoxide (6.3 mmol) in dry MeOH or EtOH (10 ml) at room temperature under argon during 5 minutes. After the addition was complete, the mixture was stirred for 24 hours and quenched with an excess of aqueous NH_4Cl (3 *M*).

4-(1-Methoxycarboethyl)-3-nitropyridine (**1b**).

From the reaction of **1a** with methyl iodide after quenching with water, a deep red byproduct (**4a**) was filtered off from the reaction mixture. The filtrate was then extracted with CH_2Cl_2 (3 x 100 ml). The organic phase was washed with brine, dried (Na_2SO_4) and stripped of solvent to give the crude product as an red oil. Flash chromatography (CH_2Cl_2) gave **1b** as an red oil, 455 mg (42%). IR (neat) max/cm^{-1}: 3360 (bs), 2954 (bs), 1738 (s), 1604 (m), 1529 (s), 1436 (m), 1354 (s); ^1H NMR (400 MHz, $CDCl_3$): 9.17 (1H, s, H-2), 8.79 (1H, d, *J* = 5.2, H-6), 7.46 (1H, d, *J* = 5.2, H-5), 4.40 (1H, q, *J* = 7.2, C**H**), 3.70 (3H, s, OC**H**$_3$), 1.63 (3H, s, *J* = 7.2, C**H**$_3$CH-); ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 153.7, 146.1, 144.0, 133.1, 123.9, 52.7, 40.9, 17.2; m/z (EI) 210.06405 (M+, $C_9H_{10}N_2O_4$ requires 210.06384), 210 (M, 8), 179 (21), 164 (100), 150 (36), 104 (38).

4-(1-Ethoxycarbopropyl)-3-nitropyridine (**1c**).

Reaction of **1a** with ethyl iodide, extraction of the product with Et_2O, drying (Na_2SO_4) and evaporation of the solvent gave a red oil, 972 mg. Purification by flash chromatography (EtOAc:cyclohexane = 1:1) gave **1c** as a light yellow oil, 644 mg (53%). IR (neat) max/cm^{-1}: 2976 (m), 2937 (m), 2878 (m), 1736 (s), 1602 (s), 1530 (s), 1461 (m),1354 (s); ^1H NMR (400 MHz, $CDCl_3$): 9.12 (1H, s, H-2), 8.76 (1H, d, *J* = 5.2, H-6), 7.52 (1H, d, *J* = 5.2,

H-5), 4.18 (3H, m, OC**H**$_2$, CH_3CH_2C**H**), 2.20 (1H, m, CH_3C**H**$_2$CH), 1.91 (1H, m, CH_3C**H**$_2$CH),1.22 (3H, t, *J* = 7.2, OCH_2C**H**$_3$), 0.98 (3H, t, *J* = 7.2, C**H**$_3CH_2CH$); ^{13}C NMR (75 MHz, $CDCl_3$): 171.0, 154.0, 147.0, 146.0, 143.5, 124.0, 61.5, 47.5, 26.0, 14.0, 12.5; m/z (EI): m/ z (EI) 238.09396 (M+, $C_{11}H_{14}N_2O_2$ requires 238.09535) 239 (M+1, 1), 193 (61), 192 (82), 165 (39), 164 (59), 149 (55), 137 (24), 117 (57), 92 (79).

4-(Methoxycarbo-benzylmethyl)-3-nitropyridine (**1d**).

The crude product from the reaction of **1a** with benzyl bromide was isolated from the quenched (water) reaction mixture by filtration to give pale brown crystals. One recrystallization ($CHCl_3$) gave pure **1d**, 595 mg (41%). mp 92.5-93.0 °C; Found: C, 62.5; H, 4.8; N, 9.5. $C_{15}H_{14}N_2O_4$ requires: C, 62.9; H, 4.9; N, 9.8; IR (KBr) max/cm^{-1}: 3444 (m), 3033 (m), 2952 (m), 1731 (s), 1599 (s), 1548 (m), 1523 (s), 1495 (m), 1355 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 9.10 (1H, s, H-2), 8.72 (1H, d, *J* = 5.2, H-6), 7.44 (1H, d, *J* = 5.2, H-5), 7.27-7.10 (5H, m, Ph), 4.61 (1H, dd, *J* = 7.6, 7.6, BnC**H**), 3.67 (3H, s, OC**H**$_3$), 3.50 (1H, dd, *J* = 13.8, 7.7, -C**H**$_2$-), 3.14 (1H, dd, *J* = 13.8, 7.7, -C**H**$_2$-); ^{13}C NMR (100 MHz, d_6-DMSO): 171.2, 153.3, 146.0, 145.4, 141.9, 137.2, 128.9, 128.6, 127.0, 124.4, 52.6, 48.1, 38.7; m/z (EI) 286 (M, 0.05%), 268 (3.5), 209 (18), 180 (17), 152 (9), 121 (34), 105 (11), 91 (100).

Methyl (1-Methyl-3-nitro-1*H*-pyridine-4-ylidene)acetate (**4a**).

The red compound was filtered off from the crude reaction mixture from the reaction of **1a** with methyl iodide after quenching with water. Recrystallisation ($CHCl_3$) gave **4a** as a cotton like solid, 31mg (3%). mp 200.0-201.0 °C; Found: C, 50.9; H, 4.8; N, 13.3. $C_9H_{10}N_2O_4$ requires: C, 51.4; H, 4.8; N, 13.3; IR (KBr) max/cm^{-1}: 3430 (bs), 3089 (m), 2944 (m), 1739 (m), 1686 (s), 1653 (s), 1560 (s), 1526 (m), 1438 (s), 1403 (s), 1324 (s); ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (1H, d, *J* = 7.9, H-6), 8.30 (1H, d, *J* = 2.0, H-2), 6.54 (1H, ddd, *J* = 8.0, 1.5, 1.5, H-5), 6.39 (1H, d, *J* = 1.0, COC**H**), 3.69 (3H, s, NC**H**$_3$), 3.56 (3H, s, OC**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 143.0, 138.0 , 134.5, 129.9, 117.0, 89.8, 50.0, 43.0; m/z (EI): 211 (M+1, 5), 210 (M, 50), 179 (33, 151 (100), 133 (17), 121 (74), 105 (17), 93 (51), 92 (14). This compound was prepared in high yield by slowly adding a mixture of **1a** (0.27 g, 1.4 mmol) and dimethyl sulfate (0. 18 ml, 2 mmol) in dry THF (15 ml) to NaH (45 mg, 2 mmol) in dry THF (15 ml) under N_2 at 20 °C. The mixture was stirred for 48 h and quenched with water (20 ml). The red precipitate (**4a**) was collected by filtration, washed and dried. Yield 0.27 g, 1.28 mmol, 93%) [9].

Methyl (1-Ethyl-3-nitro-1,4-dihydropyridine-4-ylidene)acetate (**4b**).

The red compound was filtered off from the crude reaction mixture from **1a** and ethyl iodide after quenching with water. Recrystallisation ($CHCl_3$) gave **4b** as red needles, 18mg (2%). mp 159.0-160.0°C; Found: C, 53.2; H, 5.6; N, 12.4. $C_{10}H_{12}N_2O_4$ requires: C, 53.6; H, 5.4; N, 12.5; IR (KBr) max/cm^{-1}: 3421(bs), 3089 (s), 2984 (s), 2946 (s), 1679 (s), 1649 (s), 1555 (s), 1527 (s), 1492 (m), 1471 (s), 1354 (s), 1319 (s), 1319 (s), 1268 (s); ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (1H, d, *J* = 7.9, H-6), 8.33 (1H, d, *J* = 1.9, H-2), 6.58 (1H, ddd, *J* = 8.0, 1.6, 1.6, H-5), 6.39 (1H, d, J = 1.6, COC**H**), 3.75 (2H, q, *J* = 7.6,NC**H**$_2$), 3.69 (3H, s, OC**H**$_3$), 1.46 (3H, t, *J* = 7.6, NCH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.4, 140.6, 137.2, 130.3, 131.5, 119.4, 94.0, 51.8, 50.6, 15.5; m/z (EI): 225 (M+1, 4), 224 (M, 38), 193 (34), 165 (100), 135 (95), 107 (77), 106 (17).

Formation of the Aminopyridines (**2**).

The appropiate 3-nitropyridine compound was dissolved in either methanol or ethyl acetate, Pd/C added (5%, 2.5 mole%) and the mixture exposed to hydrogen until no starting material was detectable by TLC (normally overnight). Filtration and evaporation gave the crude product in nearly quantitative yield which was used in subsequent reactions without purification. The products were purified for characterisation purposes.

3-Amino-4-(carboxymethyl)pyridine.

4-(Benzyloxycarbomethyl)-3-nitropyridine (500 mg, 1.84 mmol) was dissolved in methanol (30 ml), Pd/C 5% was added (78 mg, 2.0 mol%) and the mixture exposed to hydrogen for 4 hours. Filtering off the catalyst and removing the solvent *in vacuo* gave the crude product as a yellow solid, 188 mg (65 %). mp 136.0-137.0 °C, identified as the free carboxylic acid: IR (neat) max/cm^{-1}: 3334 (s), 3186 (s), 1652 (s), 1500 (s), 1443 (m), 1352 (s), 1257 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 7.95 (1H, s, H-2), 7.71 (1H, d, *J* = 4.94 Hz, H-6), 6.94 (1H, d, *J* = 4.94 Hz, H-5), 3.34 (2H, s, C**H**$_2$(CO)); ^{13}C NMR (100 MHz, d_6-DMSO): 171.8. 143.4, 137.3, 137.0, 125.9, 124.7, 36.0; m/z (EI) 152.05894 (M+, $C_7H_8N_2O_2$ requires 152.05857), 152 (M+, 18), 134 (30), 108 (100), 107 (38), 80 (50). When cyclisation of this compound was attempted under acidic conditions (see below) the only product was 3-amino-4-methylpyridine.

3-Amino-4-(methoxycarbomethyl)pyridine (**2a**).

A pure sample was obtained by recrystallization from $CHCl_3$ to give colorless crystals, mp 82.5-83.0 °C; Found: C, 57.53; H: 6.22; N: 16.51; $C_8H_{10}N_2O_2$ requires: C, 57.82; H, 6.07; N, 16.86. IR (KBr) max/cm^{-1}: 3333 (bs), 3211 (bs), 2953 (m), 1731 (s), 1644 (s), 1597 (m), 1567 (s), 1503 (s), 1428 (s), 1341 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 7.96 (s, 1H, H-2), 7.70 (d, 1H, *J* = 4.9, H-6), 6.92 (d, 1H, *J* = 4.9, H-5), 5.15 (2H, bs, N**H**$_2$), 3.61 (3H, s, OC**H**$_3$), 3.58 (2H, s, C**H**$_2$(CO)); ^{13}C NMR (100 MHz, $CHCl_3$): 170.8, 142.1, 139.5, 138.2, 126.6, 125.0, 52.3, 37.1; m/z (EI) 167.1 (M+1, 11%),166.1 (100), 134.1 (93), 107.1 (94), 106 (48), 80.1 (19).

3-Amino-4-(methoxycarboethyl)pyridine (**2b**).

A pure sample was obtained by flash chromatography (EtOAc) to give a light brown solid, mp 89.0-90.0 °C; IR (KBr) max/cm^{-1}: 3427 (s), 3356 (s), 3252 (m), 2980 (m), 1723 (s), 1644 (s), 1586 (s), 1563 (s), 1531 (m), 1494 (s), 1413 (s), 1354 (s), 1221 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 7,97 (1H, s, H-2), 7.72 (1H, d, *J* = 5.2, H-6), 6.85 (1H, d, *J* = 5.2, H-5), 5.23 (2H, s, N**H**$_2$), 3.92 (1H, q, *J* = 8.0, CH_3C**H**), 3.60 (3H, s, OC**H**$_3$), 1.30 (3H, d, *J* = 8.0, C**H**$_3$CH); ^{13}C NMR (100 MHz, d_6-DMSO): 173.8, 142.3, 137.7, 137.6, 130.9, 121.2, 51.9, 38.1, 16.4; m/z (EI) 180.08992 (M$^+$, $C_9H_{12}N_2O_2$ requires 180.08988) 181 (M+1, 9%), 180 (M, 81), 148 (47), 121 (100), 120 (46), 104 (13).

3-Amino-4-(1-ethoxycarbopropyl)pyridine (**2c**).

A pure sample was obtained by flash chromatograpy (MeOH:CH_2Cl_2=1:20) to give a yellow oil. IR (KBr) max/cm^{-1}: 3353 (bs), 3221 (bs), 2970 (bs), 1724 (s), 1641 (s), 1591 (m), 1562 (m), 1500 (m), 1460 (m), 1422 (s), 1370 (s), 1327 (m), 1262 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 7.97 (1H, s, H-2), 7.73 (1H, d, *J* = 4.8, H-6), 6.90 (1H, d, *J* = 4.8, H-5), 5.26 (2H, bs, N**H**$_2$),

4.08 (2H, m, OC**H**$_2$), 3.73 (1H, t, J = 7.5, CH_3CH_2C**H**), 1.87 (1H, m, CH_3C**H**$_2$CH), 1.65 (1H, m, CH_3C**H**$_2$CH), 1.14 (3H, t, *J* = 7.2, OCH_2C**H**$_3$), 0.88 (3H, t, *J* = 7.2, $CHCH_2$C**H**$_3$);^{13}C NMR (100 MHz, d_6-DMSO): 172.7, 142.6, 137.6, 137.5, 129.1, 121.3, 60.3, 45.3, 24.5, 14.0, 11.7; m/z (EI) 208.12072 (M+, $C_{11}H_{16}N_2O_2$ requires 208.12117) 209 (M+1, 11), 208 (M, 61), 180 (15), 135 (65), 134 (100), 133 (30), 119 (28), 107 (46).

3-Amino-4-(methoxycarbo-benzylmethyl)pyridine (**2d**).

A pure sample was obtained by flash chromatography (MeOH:CH_2Cl_2=1:50) to give a light yellow solid. mp 155.0-157.0 °C; IR (KBr) max/cm^{-1}: 3398 (s), 3323 (m), 3214 (s), 3020 (m), 2928 (m), 2867 (m), 1636 (s), 1595 (m), 1562 (s), 1495 (s), 1423 (s), 1299 (m); ^{1}H NMR (400 MHz, d_6-DMSO): 7.95 (1H, s, H-2), 7.71 (1H, d, *J* = 5.0, H-6), 7.24-7.15 (5H, m, Ph), 7.00 (1H, d, *J* = 5.0, H-5), 5.29 (2H, bs, N**H**$_2$), 4.22 (1H, dd, *J* = 8.7, 6.7, BnC**H**), 3.53 (3H, s, OC**H**$_3$), 3.20 (1H, dd, *J* = 14.0, 8.8, PhC**H**$_2$), 3.00 (1H, dd, *J* = 14.0, 6.6, PhC**H**$_2$); ^{13}C NMR (100 MHz, d_6-DMSO): 173.5, 143.4, 139.5, 138.7, 138.4, 129.7, 129.3, 129.0, 127.1, 122.5, 52.7, 46.0, 37.3; m/z (EI): 256.12128 (M$^+$, $C_{15}H_{16}N_2O_2$ requires 256.12117) 257 (M+1, 44%), 256 (M, 100), 225 (42), 200 (33), 166 (11), 165 (79), 133 (93), 91 (97).

3-Amino-4-(methoxycarbomethyl)-6-methoxypyridine (**2e**).

A pure sample was obtained by flash chromatography (MeOH:CH_2Cl_2 1:20) to give **2e** as a light brown solid. mp 51.5-52.5°C; IR (KBr) max/cm^{-1}: 3418 (s), 3349 (s), 2986 (m), 2948 (m), 1724 (s), 1635 (m), 1612 (m), 1502 (s), 1459 (m), 1442 (s), 1413 (s), 1395 (s), 1337 (m), 1314 (m), 1251 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 7.57 (1H, s, H-2), 6.50 (1H, s, H-5), 4.57 (2H, bs, N**H**$_2$), 3.71 (3H, s, OC**H**$_3$), 3.61 (3H, s, OC**H**$_3$), 3.59 (2H, s, C**H**$_2$); ^{13}C NMR (100 MHz, d_6-DMSO): 170.5, 156.2, 138.0, 132.4, 132.3, 110.9, 52.7, 51.8, 35.7; m/z (EI) 196.08463 (M+, $C_{11}H_{16}N_2O_2$ requires 196.08479) 197 (M+1, 7), 196 (M, 64), 195 (M-1, 23), 164 (21), 163 (48), 137 (21), 135 (45), 134 (22), 110 (18), 94 (26), 93 (29).

Formation of 6-Azaoxindoles (**3**) Under Basic Conditions.

The appropriate 3-amino-4-substituted pyridine (2.0 mmol) was dissolved in ethanol (70 ml) and sodium hydride (3.0 mmol) in ethanol (6 ml) was added. The purple solution was stirred at roomtemperature over night before water (75 ml) was added and the ethanol stripped off. Generally, the products were difficult to isolate from the aqueous solution by continous extraction and pH-adjustment to pH 7 - 8.

3-Hydroxy-3-benzyl-6-azaoxindole (**5**).

The evaporated reaction mixture was stirred with methanol (30 ml) for 2 hours before it was passed through a short column of silica. Evaporation of the solvent gave **5** (183 mg, 61%) as a yellow solid. Recrystallization (MeOH/H_2O) gave pure **5**, mp 220.0-222.0 °C; IR (KBr) max/cm^{-1}: 3281 (s), 1740 (s), 1705 (s), 1622 (m), 1495 (m), 1453 (s), 1302 (m), 1208 (s); ^{1}H NMR (400 MHz, d_6-DMSO): 10.28 (1H, bs, NH), 8.20 (1H, d, *J* = 4.9, H-6), 7.92 (1H, s, H-2), 7.13 (1H, d, *J* = 4.9, H-5), 7.12-6.85 (5H, m, Ph), 6.4 (1H, s, O**H**), 3.18 (1H, d, *J* =12.8 Hz, -C**H**$_2$-), 3.02 (1H, d, *J* = 12.8 Hz, -C**H**$_2$-); ^{13}C NMR (100 MHz, d_6-DMSO): 178.2, 143.5, 139.2, 138.2, 134.4, 130.5, 130.1, 127.6, 126.6, 119.5, 76.4, 42.8; m/z (EI) 240.08976 (M+, $C_{14}H_{12}N_2O_2$ requires 240.08987) 226 (M+, 2%), 225 (M-1,8%), 209 (28), 195 (12), 179 (41), 165 (17), 149 (32), 131 (9), 119 (26),91 (100).

Formation of 6-Azaoxindoles (**3**) Under Acidic Conditions.

a) with HCl.

The appropriate 3-amino-4-substituted pyridine (2.0 mmol) was dissolved in diethylether (15 ml) and HCl (10 ml, 10% aqueous). The resulting biphasic solution was stirred at room temperature over night. The two phases were separated and the organic phase washed with water. The combined aqueous phases were evaporated to give the crude 6-azaoxindole hydrochloride. There can be keto-enol tautomerism in all 6-aza-oxindole products, but the spectroscopic data showed the salts to exist in the enol form only.

6-Azaoxindole Hydrochloride (**3a•HCl**).

The product was obtained as a white solid, 340 mg (98%), mp 225 °C (dec.). IR (KBr) max/cm^{-1}: 3380 (bs), 3018 (bs), 1780 (s), 1644 (m), 1606 (s), 1524 (m), 1476 (s), 1445 (m), 1346 (m), 1250 (m), 1225 (m); ^{1}H NMR (400 MHz, d_6-DMSO):13.80 (1H, bs, NH), 12.50 (1H, s, OH), 8.48 (1H, s, H-7), 8.01 (1H, d, J = 6.2, H-5), 7.58 (1H, d, J = 6.4, H-4), 5.90 (s, H-3); ^{13}C NMR (100 MHz, d_6-DMSO): 162.9, 139.3, 128.9, 126.5, 121.4, 112.0, 83.1.

3-Methyl-6-azaoxindole Hydrochloride (**3b•HCl**).

The product was obtained as a white solid, 332 mg (90%), mp 232-234 °C. IR (KBr) max/cm^{-1}: 3170 (bs), 1667 (m), 1590 (s), 1444 (s), 1383 (s), 1349 (m), 1307 (m), 1262 (m), 1222 (m); ^{1}H NMR (400 MHz, d_6-DMSO): 13.8 (1H, bs, NH), 12.2 (1H, s, OH), 8.42 (1H, d, J = 5.4, H-7), 7.99 (1H, dd, J = 6.2, 5.4, H-5), 7.53 (1H, d, J = 6.2, H-4), 2.11 (s, CH_3); ^{13}C NMR (100 MHz, d_6-DMSO: 159.9 (s), 137.9 (s), 128.2 (d), 125.5 (s), 121.0 (d), 110.4 (d), 91.0 (s), 6.6 (q); m/z (EI) 148.06333 (M$^+$, $C_8H_8N_2O$ requires 148.06366), 183 (M-1, 26%), 164 (18), 148 (100), 129 (35), 120 (49), 105 (71).

3-Benzyl-6-azaoxindole Hydrochloride (**3d•HCl**).

The product precipitated from the reaction mixture, and was isolated by filtration to give a white solid, 230 mg (42%), mp 219.221 °C. IR (KBr) max/cm^{-1}: 3291 (m), 3215 (m), 3059 (m), 1670 (s), 1566 (s), 1533 (s), 1517 (s), 1494 (m), 1430 (s), 1350 (m), 1316 (m); ^{1}H NMR (400 MHz, d_6-DMSO): 13.65 (1H, bs, NH), 12.15 (1H, s, OH), 8.40 (1H, d, J = 5.6, H-7), 7.93 (1H, dd, J = 6.0, 6.4, H-5), 7.41 (1H, d, J = 6.4, H-4), 7.30-7.10 (5H, Ph), 4.00 (2H, s, PhC**H**$_2$); ^{13}C NMR (100 MHz, d_6-DMSO: 160.0, 141.6, 137.5, 128.5, 128.3, 128.1, 125.9, 125.7, 121.1, 110.2, 95.2, 27.2; m/z (EI) 224.09486 (M$^+$, $C_{14}H_{12}N_2O$ requires 224.09496), 224.1 (M+, 41%), 147.1 (4), 91.1 (100).

3,3-Dimethyl-5-methoxy-6-azaoxindole (**3f**).

5-Methoxy-6-azaoxindole (**3e**) (100 mg, 0.61 mmol) was dissolved in dry DMF (10 ml), sodium hydride (17 mg, 0.71 mmol) was added and the mixture stirred for 5 minutes. Methyl iodide (47 µl, 0.76 mmol) was added and the reaction mixture stirred at room temperature. After 24 hours another batch of sodium hydride and methyl iodide was added and stirring continued for another 24 hours. The reaction mixture was then evaporated to dryness, dissolved in ammonium chloride (15 ml, 3 *M*) and extraced with ethyl acetate (3 x 30 ml). Drying and evaporation gave the crude product as a light brown solid. One recrystallization ($CHCl_3$) gave pure **3f** as a light brown solid, 35 mg (30 %). mp 194.0-195.0 °C; IR (KBr) max/cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (1H, bs, NH), 7.75 (1H, s, H-7), 6.64 (1H, s, H-4),

3.92 (3H, s, OCH_3), 1.41 (6H, s, $2xCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 182.0, 160.3, 149.4, 131.4, 125.4, 106.1, 53.6, 44.7, 23.9; m/z (EI) 192.08979 (M+, $C_{10}H_{12}N_2O_2$ requires 192.08987) 193 (M+1, 14), 192 (M, 100), 191 (M-1, 86), 177 (12), 163 (53), 162 (16).

b) with Tetrafluorohydroboric Acid

The appropriate 3-amino-4-substituted pyridine (2.0 mmol) was dissolved in water (15 ml), HBF_4 (0.88 ml, 3.5 moleq, 50wt% in water) was added and the mixture heated at reflux for 30 minutes. When the solution had reached room temperature, it was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate. Drying (Na_2SO_4) and evaporation gave the product as a white solid.

6-Azaoxindole (**3a**).

The product was obtained as a white solid, 169 mg (63%), mp 232 °C (dec.). IR (KBr) max/cm^{-1}: 3085 (bs), 2715 (s), 1675 (s), 1584 (s), 1456 (s), 1338 (m), 1281 (m), 1209 (m), 1167 (m), 1120 (m); ^1H NMR (400 MHz, d_6-DMSO): 11.40 (0.5H, bs, enol N**H**), 10.55 (0.7H, bs, keto N**H**), 9.89 (0.7H, bs, enol-O**H**), 8.20 (1H, d, *J* = 4.8, keto H-5), 8.09 (1H, s, keto H-7), 7.30 (0.7H, d, *J* = 6.8, enol H-5), 7.27 (1H, d, keto H-4), 7.22 (0.7H, s, enol H-7), 6.58 (0.7H, d, *J* = 6.8, enol H-4), 4.94 (0.7H, s, enol H-3), 3.56 (2H, s, keto H-3); ^{13}C NMR (100 MHz, d_6-DMSO) : 175.5, 170.6, 143.0, 141.1, 140.2, 135.0, 129.9, 127.5, 127.4, 119.8, 110.0, 103.7, 85.9, 35.5; m/ z (EI) 134,04807 (M+, $C_7H_6N_2O$ requires 134.04801) 135 (13), 134 (100), 106 (30), 105 (69), 79 (24).

3-Ethyl-6-azaoxindole (**3c**).

The product was obtained as a white solid, 317 mg (98%), mp 220 °C (dec.). IR (KBr) max/cm^{-1}: 3257 (bs), 2966 (bs), 1704 (s), 1507 (s), 1560 (s), 1425 (s), 1355 (m), 1318 (m), 1276 (s); ^1H NMR (400 MHz, d_6-DMSO): 9.90 (1H, bs, N**H**), 7.23 (1H, d, *J* = 6.9, H-5), 7.15 (1H, s, H-7), 6.50 (1H, d, *J* = 6.9, H-4), 2.28 (2H, q, *J* = 7.5, -C**H**$_2$-), 1.00 (3H, t, *J* = 7.5, C**H**$_3$-); ^{13}C NMR (75 MHz, d_6-DMSO: 169.8, 135.8, 126.8, 125.9, 109.1, 101.6, 99.7, 16.0, 14.2; m/z (EI) 162.07873 (M+, $C_9H_{10}N_2O$ requires 162.07931) 163 (M+1, 6), 162 (M, 47), 134 (100), 133 (28), 119 (54), 106 (13), 105 (12).

5-Methoxy-6-azaoxindole (**3e**).

The product was obtained as a white solid, 328 mg (98%), mp 246-247 °C. IR (KBr) max/cm^{-1}: 3314 (bs), 3042 (s), 2956 (s), 2919 (s), 1712 (s), 1689 (s), 1483 (s), 1445 (s), 1367 (s), 1295 (s), 1246 (m), 1192 (m); ^1H NMR (400 MHz, d_6-DMSO): 10.37 (1H, bs, NH), 7.59 (1H, s, H-7), 6.74 (1H, s, H-4), 3.77 (3H, s, OC**H**$_3$), 3.52 (2H, s, H-3); ^{13}C NMR (100 MHz, d_6-DMSO: 175.0, 158.8, 139.9, 135.7, 124.3, 107.3, 53.0, 35.7; m/z (EI) 164.05802 (M^+, $C_8H_8N_2O_2$ requires 164,05857), 165 (M+1, 30), 164 (M, 100), 163 (M-1, 94), 136 (22), 135 (88), 134 (63), 107 (32), 94 (34), 67 (30).

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