Synthesis of Substituted Azaoxindoles for the Preparation of Aza-tenidap Analogs

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The preparation of a set of eight azaoxindoles bearing substituents on the aromatic nucleus is outlined. These compounds were required for the preparation of aza-analogs of the anti-inflammatory oxindole tenidap. Two methods of synthesis were used, the first involving the addition of malonate to 2-chloro-3-nitropyridine derivatives followed by nitro group reduction and one-pot cyclization/hydrolysis/decarboxylation. The second method, utilizing the vicarious nucleophilic substitution (VNS) reaction of nitropyridine derivatives (followed by nitro group reduction and one-pot cyclization/hydrolysis), constitutes a novel route to azaoxindoles.

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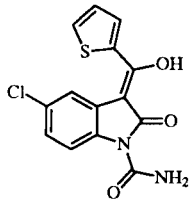
The anti-inflammatory oxindole derivative tenidap (**1**) has demonstrated excellent activity in clinical trials in rheumatoid arthritis patients [1]. In a recent program to examine the anti-inflammatory properties of azaoxindole analogs of **1**, synthetic routes to a variety of aromatic ring-substituted azaoxindoles were required. While all four unsubstituted azaoxindole nuclei are now known [2,3,4], very few azaoxindoles bearing substituents on the pyridyl ring have been reported [5]. In this paper we describe the synthesis of eight new azaoxindoles of this class, **2a-g** and **3**. Two methods of synthesis were used. The first, involving the addition of malonate to 2-chloro-3-nitropyridines, has previously been used in the synthesis of 4-azaoxindole [2] and its 5- and 7-methyl derivatives [5]. This route parallels the synthesis of oxindoles *via* addition of malonate to halonitrobenzenes [6]. The second method, beginning with the vicarious nucleophilic substitution (VNS) reaction of nitropyridines [7], constitutes a novel route to azaoxindoles. The majority of the azaoxindoles prepared were in the 4-azaoxindole series, a consequence of their ease of synthesis by the methods described here and the availability of starting materials.



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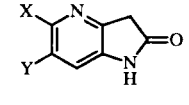
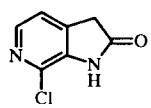


2a, X = Cl, Y = H
2b, X = Cl, Y = Cl
2c, X = H, Y = Cl
2d, X = H, Y = F
2e, X = H, Y = CF_3
2f, X = CF_3, Y = H
2g, X = MeO, Y = H



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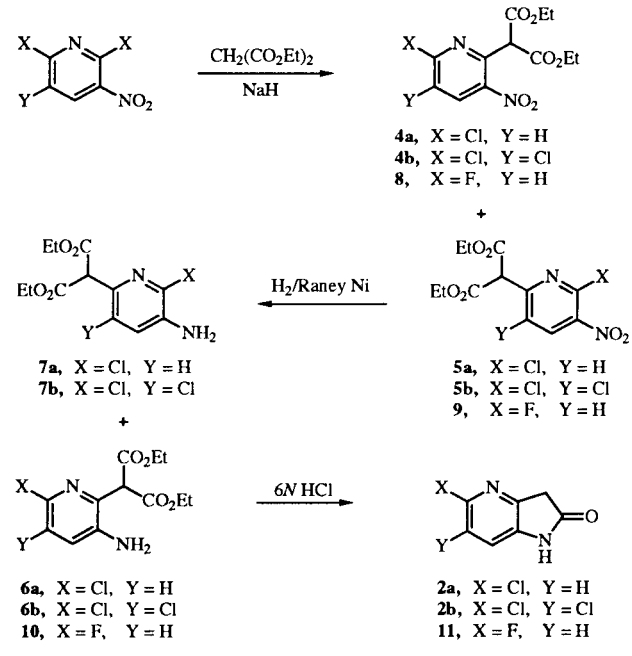
5-Chloro-4-azaoxindole (**2a**) and 5,6-dichloro-4-azaoxindole (**2b**) were prepared starting from 2,6-dichloro-3-nitropyridine and 3-nitro-2,5,6-trichloropyridine [8] respectively (Scheme 1). In both cases, competitive displacement of the 6-chloro substituent by malonate was observed [9]. Thus the reaction of 2,6-dichloro-3-nitropyridine with diethyl malonate in DMF, resulted in a 1:1 mixture of the desired 2-substituted pyridine **4a** and the 6-substituted isomer **5a**. Fortunately, switching the solvent to 1,2-dimethoxyethane (DME) altered the ratio to 2:1 in favor of the desired product. Separation of **4a** from **5a** and excess diethyl malonate proved unnecessary for successful completion of the synthesis. The mixture was hydrogenated over Raney nickel providing a mixture of amino diesters **6a** and **7a** which was directly subjected to the conditions for hydrolysis/cyclization of **6a** (6*N* HCl/reflux). Under these conditions the unwanted regioisomer **7a** presumably gives rise to 3-amino-2-chloro-6-methylpyridine which, unlike **2a**, does not precipitate on concentration of the reaction mixture and is removed by

Scheme 1



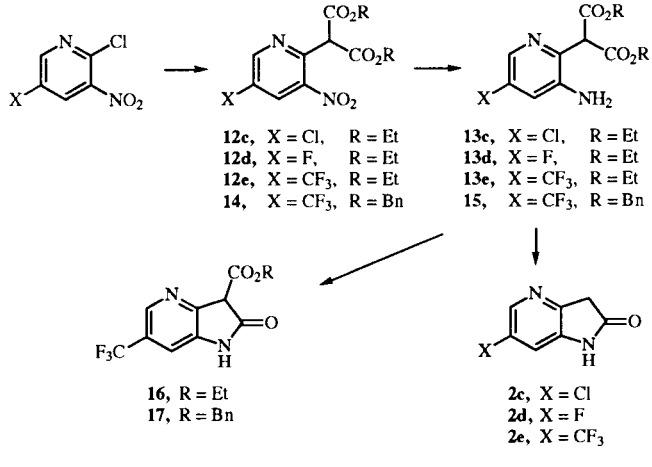
washing the desired product with water. The overall yield of **2a** from 2,6-dichloro-3-nitropyridine was 32%.

The reaction of 3-nitro-2,5,6-trichloropyridine [8] with diethyl malonate favored the unwanted 6-substituted isomer (**5b**) over the desired product (**4b**) by a ratio of 2:1 using either DMF or DME as solvent. The diester **4b,** like **4a,** was not isolated; the mixture of **4b**, **5b** and excess diethyl malonate was carried on through hydrogenation and hydrolysis to provide 5,6-dichloro-4-azaoxindole (**2b**) in 13% overall yield from 3-nitro-2,5,6-trichloropyridine.

While the reaction of diethylmalonate anion with 2,6-difluoro-3-nitropyridine favored displacement of the 2-fluoro substituent yielding a 2:1 mixture of **8** and **9**, all attempts to achieve cyclization of the reduction product **10** to 5-fluoro-4-azaoxindole (**11**) were met with failure. For example, although complete consumption of **10** took place in refluxing 6*N* HCl, no discrete product could be isolated from the reaction mixture, a result likely due to solvolytic displacement of the 4-fluoro substituent.

As expected, exclusive displacement of the 2-chloro substituent took place in the reactions of malonate with 2,5-dichloro-3-nitropyridine [10] and 2-chloro-5-fluoro-3-nitropyridine [11] and as a result, the respective syntheses of 6-chloro-4-azaoxindole (**2c**) and 6-fluoro-4-azaoxindole (**2d**) were relatively straightforward (Scheme 2). For the preparation of **2d**, however, it was important to use DMF and not DME as solvent for the malonate addition step due to the formation of a number of unidentified side products in the latter solvent.

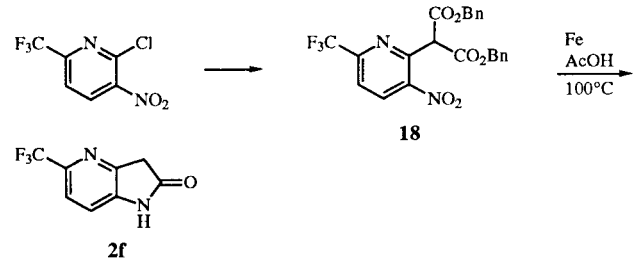
Scheme 2



Based on the experience with the synthesis of azaoxindoles **2c** and **2d**, the preparation of 6-trifluoromethyl-4-azaoxindole (**2e**) was expected to proceed uneventfully *via* malonate displacement on 2-chloro-3-nitro-5-trifluoromethylpyridine [12] (Scheme 2). This was not the case, however, since aminodiester (**13e**), upon exposure to the conditions for hydrolysis/cyclization, underwent a substantial degree of double decarboxylation giving 3-amino-2-methyl-5-trifluoromethylpyridine. Additionally, 3-carboethoxy-6-trifluoromethyl-4-azaoxindole (**16**) was formed along with the desired product **2e** which was isolated in low yield (35%). To try to circumvent the problem of double decarboxylation, **16** (prepared in high yield by heating **13e** in xylene) was subjected to the hydrolysis conditions, but again significant formation of 3-amino-2-methyl-5-trifluoromethylpyridine occurred. A somewhat better overall yield was obtained using 3-carbobenzyloxy-6-trifluoromethyl-4-azaoxindole (**17**) which underwent hydrogenolysis and thermal decarboxylation to **2e** in 43% yield. The intermediate **17** was prepared in a manner analogous to that for **16** except that cyclization of the aminodiester **15** to **17** occurred under the conditions used to reduce the nitro group of **14** (Fe/AcOH/100°).

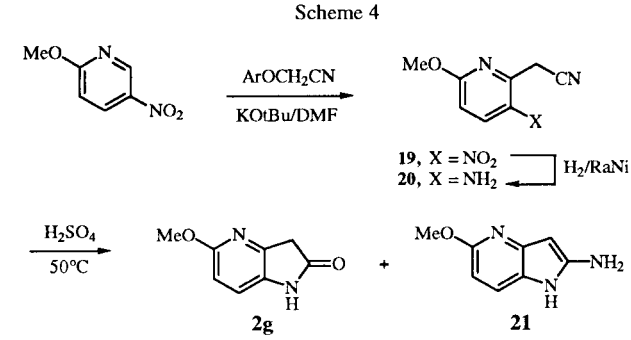
In anticipation of complications similar to those encountered in synthesis of 6-trifluoromethyl-4-azaoxindole (**2e**), the synthesis of 5-trifluoromethyl-4-azaoxindole (**2f**) was carried out *via* the dibenzyl ester **18**, starting from 2-chloro-3-nitro-6-trifluoromethylpyridine [13] (Scheme 3). In contrast to the reduction of **14**, exposure of **18** to Fe in hot AcOH gave the desired azaoxindole **2f** directly in moderate yield (52%).

Scheme 3



The synthesis of 5-methoxy-4-azaoxindole (**2g**) illustrates a new route to azaoxindoles which involves vicarious nucleophilic substitution of hydrogen (VNS) (Scheme 4). Thus, the VNS reaction of 2-methoxy-5-nitropyridine with (4-chlorophenoxy)acetonitrile and subsequent reduction of the product **19** provided (3-amino-6-

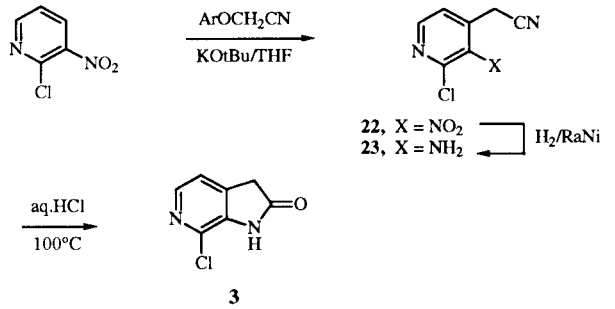
Scheme 4



methoxy-2-pyridyl)acetonitrile (**20**) as previously reported [14]. Some difficulty was encountered in finding acceptable conditions for the subsequent hydrolysis/-cyclization of **20** to the azaoxindole **2g**. The major product isolated when heating **20** in 6*N* or 12*N* HCl was 2-amino-5-methoxy-4-azaindole (**21**) as was the case using aqueous sulfuric acid. Strong heating in acid led to substantial decomposition (formation of dark material), presumably due to hydrolysis of the methoxy group and air oxidation of the resulting hydroxy compound. Warming **20** in concentrated sulfuric acid, however, did favor formation of the azaoxindole (**2g:21** = 9:7) which was isolated in 38% yield. To avoid the problem of azaindole formation, a route involving the VNS reaction of 2-methoxy-5-nitropyridine with *t*-butyl (phenylthio)-acetate was briefly investigated but the yield of the VNS product [*t*-butyl (3-nitro-6-methoxy-2-pyridyl)acetate] was low in comparison to that for obtaining **19**.

The VNS reaction of other substituted pyridines was investigated to obtain azaoxindoles with substitution patterns difficult to achieve by other means. The reaction of 2-chloro-3-nitropyridine with (4-chlorophenoxy)acetonitrile, although low yielding, gave (2-chloro-3-nitro-4-pyridyl)acetonitrile (**22**) as the only substitution product (27%) (Scheme 5) [15]. Raney nickel-catalyzed hydrogenation of **22** provided the aminonitrile **23** which was cleanly cyclized to 7-chloro-6-azaoxindole (**3**) in 6*N* HCl. Unlike the case with the cyclization of **20** to **2g**, azaindole formation was not observed.

Scheme 5



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In another unsuccessful attempt to prepare 5-fluoro-4-azaoxindole (**11**), the VNS reaction of 2-fluoro-5-nitropyridine with *t*-butyl (phenylthio)acetate was attempted. Not unexpectedly, although VNS reaction did take place, displacement of fluorine by thiophenoxide also occurred yielding *t*-butyl (3-nitro-6-phenylthio-2-pyridyl)acetate in 45% yield.

The ^{1}H nmr spectra of **2a-g** and **3** in DMSO-d_6 revealed that, with the exception of **2e**, the compounds exist solely in this solvent as the azaoxindole tautomer (2 H methylene singlet at 3.5 to 3.8 ppm). In contrast, the spectrum of **2e** showed two tautomers to be present in a 1:1 ratio: the azaoxindole tautomer (methylene singlet at 3.73 ppm) and the 2-hydroxyazaindole tautomer (singlet at 5.0 ppm; broad singlet due to OH at 12.5 ppm).

Conversion of **2a-g** and **3** to the corresponding aza-tenidap analogs was, in general, relatively straightforward. This was normally achieved by condensation of the azaoxindole with ethyl 2-thiophenecarboxylate (NaOEt/-EtOH) followed by reaction of the intermediate 3-acyl azaoxindole derivative with chlorosulfonyl isocyanate (acetonitrile/0°).

EXPERIMENTAL

All reactions requiring anhydrous were carried out in dry glassware under an atmosphere of nitrogen. The ^{1}H nmr spectra were recorded at 300 MHz (Bruker AC300 or Varian XL-300). The ir spectra were recorded on a Nicolet 510 (FT IR) spectrophotometer using potassium bromide pellets except where otherwise indicated. The low resolution mass spectra (EI) were obtained on a Finnegan EI-CI mass spectrometer. Melting points are uncorrected.

5-Chloro-4-azaoxindole (**2a**).

A solution of diethyl malonate (49.3 ml, 0.325 mole) in DME (175 ml) was added dropwise to a mechanically stirred suspension of sodium hydride (7.7 g, 0.32 mole) in dry 1,2-dimethoxyethane (DME) (350 ml). The mixture was stirred at room temperature for 1 hour and then a solution of 2,6-dichloro-3-nitropyridine (25 g, 0.13 mole) in DME (175 ml) was added to give a dark red solution. After stirring at room temperature for 18 hours, the reaction mixture was poured into water and acidified to *p*H 3 with 6*N* HCl solution. The mixture was then extracted with ether. The ether phase was washed with brine, dried over magnesium sulfate and concentrated to leave a yellow oil. Most of the excess diethyl malonate was removed by heating at 60° under high vacuum. As determined by ^{1}H nmr, the remaining oil consisted of the desired product **4a**, **5a** and diethyl malonate; the ratio of **4a** to **5a** was 2:1. The mixture was chromatographed on silica gel using 4:1 hexane/ethyl acetate as eluant. All fractions containing **4a** were combined and concentrated to yield an oil (40.5 g) containing **4a**, **5a** and diethyl malonate in a molar ratio of approximately 10:4:3; **4a** ^{1}H nmr (deuteriochloroform): δ 8.44 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 5.47 (s, 1H); **5a** ^{1}H nmr: δ 8.25 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 4.99 (s, 1H). Both compounds exhibited ethyl CH_2 and CH_3 signals at δ 4.3 and 1.3 respectively.

The mixture of **4a**, **5a** and diethyl malonate was dissolved in ethanol (300 ml) and added to a suspension of 50% Raney nickel in water (26 g) diluted with ethanol (700 ml). The mixture was hydrogenated in a Parr shaker at 3 atmospheres pressure for 4 hours and then filtered through celite to remove the catalyst. The solvent was evaporated to leave a mixture of **6a**, **7a** and diethyl malonate as a waxy solid (35.7 g); **6a** ^{1}H nmr (deuteriochloroform): δ 8.09 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 4.94 (s, 1H), plus signals at δ 4.3 (NH_2, CH_2) and 1.3 (CH_3) overlapping with the corresponding signals from other components of the mixture. The isomer **7a** displayed a methine singlet at δ 4.80.

The mixture of **6a**, **7a** and diethyl malonate was taken up in 6*N* HCl solution (700 ml) and heated at reflux for 5 hours. After removing the aqueous acid *in vacuo*, the residue was taken up in water and again concentrated to yield 5-chloro-4-azaoxindole (**2a**) as a brown solid which was dried in the air, 7.04 g (32% overall from 2,6-dichloro-3-nitropyridine). An analytical sample was prepared by recrystallization from isopropanol, mp 250-254° dec; ^{1}H nmr (DMSO-d_6): δ 10.63 (br s, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 3.61 (s, 2H); ir: 1706, 1610, 1424 cm^{-1}; ms: m/z 170 (37), 168 (100), 142 (11), 140 (25), 115 (7), 113 (15), 105 (28).

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.22. Found: C, 49.55; H, 2.95; N, 16.29.

5,6-Dichloro-4-azaoxindole (**2b**).

Diethyl malonate (24.7 ml, 0.18 mole) was added dropwise to a mechanically stirred suspension of sodium hydride (4.8 g, 0.2 mole) in dry DMF (90 ml). The mixture was stirred at room temperature for 0.25 hours and was then cooled to 0°. A cold solution of 3-nitro-2,5,6-trichloropyridine [8] (12.5 g, 55 mmoles) in DMF (40 ml) was added dropwise and the mixture was stirred at 0° for 0.25 hour. The reaction mixture was poured into water, acidified to *p*H 3 with 6*N* HCl solution and extracted with ether. The extract was washed with brine, dried over magnesium sulfate and concentrated to leave an oil which was passed through a thick pad of silica gel washing first with hexane and then ethyl acetate to elute the mixture of products. Following evaporation of the solvent, the mixture was chromatographed on silica gel using 19:1 hexane/ethyl acetate as eluant. All fractions containing **4b** were combined and concentrated to leave an oil (39.3 g) containing the desired product **4b** (5.2 g), **5b** (10.4 g) and diethyl malonate; **4b**: ^{1}H nmr: (DMSO-d_6): δ 8.55 (s, 1H), 5.40, (s, 1H); **5b**: ^{1}H nmr: δ 8.26 (s, 1H), 5.13 (s, 1H). Both compounds exhibited ethyl CH_2 and CH_3 signals at δ 4.3 and 1.3 respectively.

The mixture of **4b**, **5b** and diethyl malonate was dissolved in ethanol (100 ml) and added to a suspension of 50% Raney nickel in water (30 g) diluted with ethanol (10 ml). The mixture was hydrogenated in a Parr shaker at 3 atmospheres pressure for 5 hours and then filtered through celite to remove the catalyst. The solvent was evaporated and the residue was chromatographed on silica gel eluting with 4:1 hexane/ethyl acetate. All fractions containing the desired product **6b** which eluted slightly ahead of the isomer **7b**, were combined and concentrated to leave an oil containing **6b**: (3.2 g) and **7b**: (4.0 g); **6b** ^{1}H nmr (deuteriochloroform): δ 7.11 (s, 1H), 4.88 (s, 1H); **7b** ^{1}H nmr: δ 7.02 (s, 1H), 4.97 (s, 1H). Both compounds exhibited signals at δ 4.3 (NH_2, CH_2) and 1.3 (CH_3).

The mixture of **6b** and **7b** was taken up in 6*N* HCl solution (120 ml) and heated at reflux for 3 hours. After removing the aqueous acid *in vacuo*, the residue was taken up in ethanol and again concentrated to leave a brown solid. This was chromatographed on silica gel using 9:1 chloroform/methanol as eluant. All fractions containing the desired product were combined and concentrated. The residue was triturated with cold methanol leaving 5,6-dichloro-4-azaoxindole (**2b**) as a yellow solid, 1.42 g (13% overall from 3-nitro-2,5,6-trichloro-pyridine). An analytical sample was prepared by recrystallization from methanol, mp 230-233°; ^{1}H nmr (DMSO-d_6): δ 7.40 (s, 1H), 3.64 (s, 2H); ir: 1760, 1715, 1610, 1425 cm^{-1}; ms: m/z 206 (10), 204 (64), 202 (100), 176 (28), 174 (42), 139 (42).

Anal. Calcd. for $C_7H_4C_{12}N_2O$: C, 41.41; H, 1.99; N, 13.80. Found: C, 41.31; H, 1.73; N, 13.61.

6-Chloro-4-azaoxindole (**2c**).

The reaction of 2,5-dichloro-3-nitropyridine [10] with diethyl malonate was carried out as described above for the preparation of **4a** (synthesis of **2a**); sodium hydride (2.4 g, 0.10 mole) in DME (125 ml), diethyl malonate (15.7 ml, 0.10 mole) in DME (50 ml) and 2,5-dichloro-3-nitropyridine (10.0 g, 51.8 mmoles) in DME (75 ml). After workup, the crude product was chromatographed on silica gel using 9:1 hexane/ethyl acetate as eluant. All fractions containing the desired product were combined and concentrated to yield **12c** as an oil, 13.6 g (82%); ^{1}H nmr (DMSO-d_6): δ 7.99 (d, J = 1 Hz, 1H), 7.78 (d, J = 1 Hz, 1H), 5.58 (s, 1H), 4.12-3.14 (m, 4H), 1.18 (t, J = 7 Hz, 6H).

The sample of **12c** in ethanol (200 ml) was added to a suspension of 50% Raney nickel in water (8.8 g) diluted with ethanol (300 ml). The mixture was hydrogenated in a Parr shaker at 3 atmospheres pressure for 4 hours and then filtered through celite to remove the catalyst. The solvent was evaporated to leave **13c** as a light yellow solid (12.6 g); ^{1}H nmr (DMSO-d_6): δ 7.66 (d, J = 1Hz, 1H), 7.02 (d, J = 1Hz, 1H), 5.53 (br s, 2H), 5.08 (s, 1H), 4.12-4.04 (m, 4H), 1.12 (t, J = 7 Hz, 6H).

The sample of **13c** in 6*N* HCl (325 ml) was heated at reflux for 4 hours. The aqueous acid was evaporated and the residue was taken up in water. The resulting mixture was filtered to remove a small amount of insoluble black material. On adjustment of the filtrate *p*H to 6.5 with solid sodium bicarbonate, 6-chloro-4-azaoxindole (**2c**) precipitated as a tan solid (2.6 g) which was collected by filtration. The filtrate was extracted three times with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated to yield more 6-chloro-4-azaoxindole (3.6 g), total yield 6.2 g (71% overall from 2,5-dichloro-3-nitropyridine). An analytical sample was prepared by recrystallization from ethanol, mp >250°; ^{1}H nmr (DMSO-d_6): δ 10.68 (br s, 1H), 8.07 (s, 1H), 7.18 (s, 1H), 3.58 (s, 2H); ir: 1750, 1715, 1695, 1610, 1580, 1450, 1425 cm^{-1}; ms: m/z 170 (25), 168 (100), 140 (27), 115 (10), 113 (26), 105 (23).

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.22. Found: C, 49.77; H, 2.81; N, 16.37.

5-Fluoro-2-hydroxy-3-nitropyridine.

5-Fluoro-2-hydroxypyridine [16] (11.16 g, 98.7 mmoles) was added in portions to concentrated sulfuric acid (90 ml) at 0°. Fuming nitric acid was added dropwise. The reaction mixture was allowed to warm to room temperature and was then heated at 55-60° for 3.5 hours. After cooling to room temperature, the mixture was poured into ice/water. The precipitated 5-fluoro-2-hydroxy-3-nitropyridine, 8.24 g (53%), was collected by filtration, washed with water and dried in the air. The *p*H of the filtrate was adjusted to 2 by the addition of solid sodium bicarbonate. The solution was extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated to yield more of the desired product, 1.71 g (11%), mp >250°; ^{1}H nmr (DMSO-d_6): δ 12.92 (br s, 1H), 8.61 (dd, J = 3.5, 7.6 Hz, 1H), 8.23-8.21 (m, 1H); ir: 3070 (br), 1702, 1601, 1553, 1511 cm^{-1}; ms: m/z 158 (100), 112 (56), 100 (76), 84 (73), 57 (86).

Anal. Calcd. for $C_5H_3FN_2O_3$: C, 37.99; H, 1.91; N, 17.72. Found: C, 37.40; H, 1.73; N, 17.23.

6-Fluoro-4-azaoxindole (**2d**).

To a mixture of phosphorus pentachloride (18.2 g, 87.4 mmoles) and phosphorus oxychloride (8.1 ml, 87.3 mmoles) at 60° was added in portions 5-fluoro-2-hydroxy-3-nitropyridine (12.56 g, 79.4 mmoles). The mixture was stirred in an oil bath at 100° under nitrogen overnight, cooled to room temperature and poured into ice. After addition of more water and ethyl acetate, the mixture was filtered through celite to remove dark insoluble material. The organic phase was washed with brine, filtered again to remove more dark material, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel eluting with chloroform. Fractions containing 2-chloro-5-fluoro-3-nitropyridine were combined and concentrated to provide a yellow oil (5.21 g, 37%) which solidified on standing at 5° overnight; ^{1}H nmr (deuteriochloroform): δ 8.51 (d, J = 3 Hz, 1H), 8.01 (dd, J = 3, 6.6 Hz, 1H).

The reaction of 2-chloro-5-fluoro-3-nitropyridine with diethyl malonate was carried out as described above for the preparation of **4b** (synthesis of **2b**): sodium hydride (1.85 g, 77.1 mmoles) in DMF (100 ml), diethyl malonate (11.8 ml, 77.7 mmoles) and 2-chloro-5-fluoro-3-nitropyridine (5.21 g, 29.5 mmoles) in DMF (40 ml). After workup (using ethyl acetate for extraction), the crude product was chromatographed on silica gel using 7:3 hexane/ethyl acetate as eluant. All fractions containing the desired product were combined and concentrated to yield an oil (11.5 g) containing **12d** and diethyl malonate in a molar ratio of 11:9; **12d:** ^{1}H nmr (deuteriochloroform): δ 8.68 (d, J = 2.7 Hz, 1H), 8.21 (dd, J = 2.7, 7.7 Hz, 1H), 5.45 (s, 1H), 4.30 (q, J = 8 Hz, 4H), 1.28 (t, J = 7.8 Hz, 6H).

The mixture of **12d** and diethyl malonate was dissolved in ethanol (100 ml) and added to a suspension of 50% Raney nickel in water (7.8 g) diluted with ethanol (150 ml). The mixture was hydrogenated in a Parr shaker at 3 atmospheres pressure overnight and then filtered through celite to remove the catalyst. The solvent was evaporated to leave a mixture of **13d** and diethyl malonate as an oil; **13d:** ^{1}H nmr (deuteriochloroform): δ 7.83-7.82 (m, 1H), 6.73-6.69 (m, 1H), 4.91 (s, 1H), 4.37 (br s, 2H), 4.26-4.16 (m, 4H), 1.24 (t, J = 8 Hz, 6H).

The mixture containing **13d** and diethyl malonate was taken up in 6*N* HCl solution (280 ml) and heated at reflux for 3 hours. The aqueous acid was then evaporated. The residue was taken up in water and concentrated to leave a solid. This was taken up in dry ethanol and concentrated to leave a light green solid which was first triturated with hot ethyl acetate and then chromatographed on silica gel eluting with 9:1 chloroform/methanol. Clean fractions of the desired product were combined and concentrated to yield 6-fluoro-4-azaoxindole (**2d**) as a yellow solid, 2.95 g (75% overall from 2-chloro-5-fluoro-3-nitropyridine). An analytical sample was prepared by recrystallization from toluene/methanol, mp 189-192°; ^{1}H nmr (DMSO-d_6): δ 10.86 (br s, 1H), 8.03-8.01 (m, 1H), 7.07 (dd, J = 2, 8 Hz, 1H), 3.56 (s, 2H); ir: 1760, 1715, 1620, 1590, 1500, 1435, 1420 cm^{-1}; ms: m/z 153 (28), 152 (100), 124 (38), 123 (45), 97 (62).

Anal. Calcd. for $C_7H_5FN_2O$: C, 55.27; H, 3.31; N, 18.41. Found: C, 55.02; H, 3.11; N, 18.01.

2-Bis(carbobenzyloxy)methyl-3-nitro-5-trifluoromethylpyridine (**14**).

To a mixture of phosphorus pentachloride (11.2 g, 53.8 mmoles) and phosphorus oxychloride (5.0 ml, 54.6 mmoles) at 60° was added in portions 2-hydroxy-3-nitro-5-trifluoromethylpyridine [17] (10.3 g, 49.5 mmoles). The mixture was stirred in an oil bath at 80° under nitrogen overnight, cooled to room temperature and poured into ice. The mixture was extracted with ether. The ether extract was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using chloroform as eluant. Fractions containing the desired product, 2-chloro-3-nitro-5-trifluoromethylpyridine, were combined and concentrated to provide a brown oil (7.45 g, 66%); ^{1}H nmr (deuteriochloroform): δ 9.19 (d, J = 1.9 Hz, 1H), 9.07 (dd, J = 1.9 Hz, 1H).

The reaction of 2-chloro-3-nitro-5-trifluoromethylpyridine with dibenzyl malonate was carried out as described above for the preparation of **4a** (synthesis of **2a**): sodium hydride (1.55 g, 64.6 mmoles) in DME (60 ml), dibenzyl malonate (16.2 ml, 64.8 mmoles) in DME (45 ml) and 2-chloro-3-nitro-5-trifluoromethylpyridine (7.4 g, 32.7 mmoles) in DME (45 ml). After workup, the crude product was chromatographed on silica gel using toluene as eluant. All fractions containing the desired product were combined and concentrated to yield the diester **14** as an off-white crystalline solid, 13.2 g (87%). An analytical sample was prepared by recrystallization from toluene/hexane, mp 85-87°; ^{1}H nmr (DMSO-d_6): δ 9.35 (d, J = 1.4 Hz, 1H), 8.99 (d, J = 1.4 Hz, 1H), 7.33 (s, 10 H), 5.96 (s, 1H), 5.23 (AB d, 4H); ir: 1755, 1745, 1625, 1575, 1545 cm^{-1}; ms: m/z 475 (3), 340 (7), 277 (57), 233 (59), 107 (91), 91 (100).

Anal. Calcd. for $C_{23}H_{17}F_3N_2O_6$: C, 58.23; H, 3.61; N, 5.91. Found: C, 58.14; H, 3.30; N, 5.88.

3-Carbobenzyloxy-6-trifluoromethyl-4-azaoxindole (**17**).

A mixture of **14** (13.2 g, 27.8 mmoles) and iron dust (5.4 g, 97.3 mmoles) in glacial acetic acid (500 ml) was heated at reflux for 2 hours. After cooling, the mixture was poured over ice. The precipitate was collected by filtration, triturated with ether and air dried to leave **17** as a tan solid, 6.8 g (73%). An analytical sample was obtained by recrystallization from ethanol, mp >250°C; ^{1}H nmr (DMSO-d_6): 13.00 br s (1 H), 10.72 (br s, 1 H), 7.83 (br s, 1 H), 7.60-7.20 (br m, 5 H), 7.10 (br s, 1 H), 5.30 (br s, 2 H); ir: 1725, 1705, 1660, 1615, 1540 cm^{-1}; ms: m/z 336 (3), 202 (4), 108 (12), 91 (100).

Anal. Calcd. for $C_{16}H_{11}F_3N_2O_3$: C, 57.15; H, 3.30; N, 8.33. Found: C, 56.74; H, 3.34; N, 8.22.

6-Trifluoromethyl-4-azaoxindole (**2e**).

A solution of **17** (1.37 g, 4.07 mmoles) in acetic acid (50 ml) was hydrogenated over 10% Pd/C (500 mg) in a Parr shaker at 3 atmospheres pressure for 3 hours. The catalyst was removed by filtration and was washed extensively with warm methanol. The filtrate was concentrated under vacuum to leave a purple solid which was taken up in ethanol (75 ml). The resulting mixture was heated at reflux for 1.5 hours and the solvent was evaporated. The residue was chromatographed on silica gel using 19:1 chloroform/methanol as eluant. Clean fractions containing the desired product were combined and concentrated to leave 6-trifluoromethyl-4-azaoxindole (**2e**) as a tan solid, 349 mg (43%). An analytical sample was prepared by recrystallization from chloroform, mp 208-210°; ^{1}H nmr (DMSO-d_6): 12.50 (br s, 0.5 H), 10.83 (br s, 0.5 H), 10.30 (br s, 0.5 H), 8.45 (s, 0.5 H), 7.76 (s, 0.5 H), 7.33 (s, 0.5 H), 6.63 (s, 0.5 H), 5.00 (s, 0.5 H), 3.73 (s, 1H); ir: 1755, 1720, 1630, 1580, 1510, 1420 cm^{-1}; ms: m/z 202 (100), 183 (20), 174 (43), 173 (43), 147 (46), 127 (17), 105 (33).

Anal. Calcd. for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86. Found: C, 47.07; H, 2.57; N, 13.74.

2-Bis(carbobenzyloxy)methyl-3-nitro-6-trifluoromethylpyridine (**18**).

To a solution of 2-hydroxy-6-trifluoromethylpyridine [18] (9.8 g, 60.1 mmoles) in concentrated sulfuric acid (90 ml) was added fuming nitric acid (9 ml). The mixture was heated in an oil bath at 50° for 18 hours and then poured into ice/water. After stirring for 0.5 hour the mixture was extracted with chloroform. The organic extract was dried over magnesium sulfate and concentrated to leave a yellow oil (10.5 g) containing 2-hydroxy-3-nitro-6-trifluoromethylpyridine [^{1}H nmr (DMSO-d_6): δ 8.56 (d, J = 8.6 Hz, 1 H), 7.49 (d, J = 8.6 Hz, 1 H)], 2-hydroxy-5-nitro-6-trifluoromethylpyridine [^{1}H nmr: δ 8.41 (d, J = 8 Hz, 1 H), 7.09 (d, J = 8 Hz, 1 H)] and 3,5-dinitro-2-hydroxy-6-trifluoromethylpyridine [^{1}H nmr: δ 8.83 (s, 1 H)] in a molar ratio of 65:25:10 respectively.

The oil was combined in dry flask with phosphorus pentachloride (15.6 g, 74.9 mmoles) and phosphorus oxychloride (6.8 ml, 74.3 mmoles) and the resulting mixture was heated in an oil bath at 90° for 18 hours. After cooling to room temperature, the mixture was poured into ice/water and was extracted with ether. The organic extract was dried over magnesium sulfate and concentrated to leave a yellow oil. This was chromatographed on silica gel eluting with 2:1 chloroform/hexane. All fractions containing 2-chloro-3-nitro-6-trifluoromethylpyridine were combined and concentrated to an oil from which a small amount of 2-chloro-3,5-dinitro-6-trifluoromethylpyridine crystallized. The supernatant (4.0 g) was separated containing 2-chloro-3-nitro-6-trifluoromethylpyridine, [^{1}H nmr (deuteriochloroform): δ 8.35 (d, J = 8.6 Hz, 1 H), 7.82 (d, J = 8.6 Hz, 1 H)], 2-chloro-5-nitro-6-trifluoromethylpyridine [^{1}H nmr: δ 8.18 (d, J = 8 Hz, 1 H), 7.71 (d, J = 8 Hz, 1 H)] and 2-chloro-3,5-dinitro-6-trifluoromethylpyridine [^{1}H nmr: δ 8.77 (s, 1 H)] in a molar ratio of 65:20:15 respectively.

A solution of dibenzyl malonate (3.3 ml, 13.2 mmoles) in DMF (15 ml) was added dropwise to a slurry of 60% NaH/oil (0.51 g, 12.8 mmoles) in DMF (20 ml). The mixture was stirred at room temperature for 1 hour and then a portion (1.5 g) of the above nitropyridine mixture [containing approximately 0.94 g (4.1 mmoles) 2-chloro-3-nitro-6-trifluoromethylpyridine] in DMF (15 ml) was added dropwise. The reaction mixture was stirred at room temperature for 18 hours and then poured into ice/water. The mixture was acidified with 6*N* HCl solution and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and concentrated to an oil which was chromatographed on silica gel eluting with toluene. Clean fractions containing the desired product were combined and concentrated to afford **18** as a crystalline solid, 1.80 g (17% overall from 2-hydroxy-6-trifluoromethylpyridine), mp 90-92°; ^{1}H nmr (deuteriochloroform): δ 8.62 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 7.30 (s, 10 H), 5.66 (s, 1 H), 5.23 (s, 4 H); ir (chloroform): 1751, 1741, 1606, 1534 cm^{-1}; ms: m/z 475 (1), 277 (44), 233 (37), 107 (63), 91 (100).

Anal. Calcd. for $C_{23}H_{17}F_3N_2O_6$: C, 58.23; H, 3.61; N, 5.91. Found: C, 58.60; H, 3.44; N, 5.82.

5-Trifluoromethyl-4-azaoxindole (**2f**).

A mixture of **18** (1.5 g, 3.16 mmoles), iron powder (0.61 g, 10.9 mmoles) and glacial acetic acid (50 ml) was heated in an oil bath at 100° for 18 hours. After cooling, the mixture was filtered washing with additional acetic acid. The filtrate was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel eluting first with chloroform and then with 98:2 chloroform/methanol. Clean fractions containing the desired product were combined and concentrated to afford **2f** as a solid, 0.33 g (52%). An analytical sample was prepared by recrystallization from chloroform, mp 213-216°; ^{1}H nmr (DMSO-d_6): 10.92 (br s, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.27 (d, J = 8 Hz, 1 H), 3.71 (s, 2 H); ir: 1760, 1715, 1620, 1595 cm^{-1}; ms: m/z 202 (100), 183 (25), 182 (25), 174 (40), 173 (50), 147 (36), 127 (18), 105 (61), 78 (57).

Anal. Calcd. for $C_8H_5F_3N_2O$: C, 47.54; H, 2.49; N, 13.86. Found: C, 47.50; H, 2.31; N, 13.72.

5-Methoxy-4-azaoxindole (**2g**).

A solution of (3-amino-6-methoxy-2-pyridyl)acetonitrile (**20**) [14] (1.70 g, 10.4 mmoles) in concentrated sulfuric acid (170 ml) was warmed at 50° for 5 days. After cooling, the mixture was poured into ice and neutralized by addition of solid NaOH while cooling in an ice bath. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate and evaporated to leave a yellow solid which, by ^{1}H nmr consisted of a mixture of the azaoxindole **2g** and the azaindole **21** in a molar ratio of 9:7. The material was chromatographed on silica gel eluting with ethyl acetate. Clean fractions containing the desired product were combined and concentrated to leave 5-methoxy-4-azaoxindole (**2g**) as a white solid, 650 mg (38%). An analytical sample was prepared by recrystallization from ethyl acetate/cyclohexane, mp 212-214°; ^{1}H nmr (DMSO-d_6): δ 10.23 (br s, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 3.77 (s, 3H), 3.52 (s, 2H); ir: 1720, 1690, 1610, 1600, 1480, 1460, 1420 cm^{-1}; ms: m/z 164 (100), 149 (5), 136 (18), 135 (18), 121 (15), 80 (45).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.55; H, 4.65; N, 17.24.

2-Amino-5-methoxy-4-azaindole (**21**).

This compound had ^{1}H nmr (DMSO-d_6): δ 9.94 (br s, 1 H), 7.17 (d, J = 8.2Hz, 1 H), 6.03 (d, J = 8.2Hz, 1 H), 5.52 (br s, 2H), 5.19 (s, 1 H), 3.72 (s, 3H); ir: 1645, 1630, 1580, 1450, 1415 cm^{-1}; ms: m/z 163 (100), 162 (55), 148 (11), 134 (29), 120 (15).

(2-Chloro-3-nitro-4-pyridyl)acetonitrile (**22**).

To a stirred solution of potassium *tert*-butoxide (11.37 g, 101 mmoles) in anhydrous tetrahydrofuran (70 ml) at -78°, a solution of 2-chloro-3-nitropyridine (7.30 g, 46.0 mmoles) and (4-chlorophenoxy)acetonitrile (8.49 g, 50.7 mmoles) in anhydrous tetrahydrofuran (70 ml) was added dropwise at such a rate that the reaction temperature was maintained below -50°. The resulting purple reaction mixture was stirred at -78° for 1 hour at which time glacial acetic acid (9 ml)) was added. The mixture was allowed to warm to room temperature and a solution of 5% HCl (50 ml) was then added. After extracting with ether and twice with methylene chloride, the combined extracts were dried (magnesium sulfate) and concentrated *in vacuo* to afford an oil which was chromatographed on silica gel eluting successively with chloroform and 9:1 chloroform/methanol. Fractions containing the desired product were combined and concentrated to leave a solid. This was recrystallized from ether/hexane to provide (2-chloro-3-nitro-4-pyridyl)acetonitrile (**22**) as a yellow

crystalline solid, 2.42 g (27%), mp 85-87°; ^{1}H nmr (deuteriochloroform) δ 8.60 (d, J = 4.8 Hz, 1 H), 7.62 (d, J = 4.8 Hz, 1 H), 3.84 (s, 2 H); ir: 2260, 1595, 1550, 1540, 1460, 1410, 1390, 1360 cm^{-1}; ms: m/z 199 (19), 197 (57), 153 (41), 151 (100), 126 (40), 124 (60), 116 (36), 115 (45), 63 (88).

Anal. Calcd. for $C_7H_4ClN_3O_2$: C, 42.55; H, 2.04; N, 21.27. Found: C, 42.65; H, 1.98; N, 21.19.

7-Chloro-6-azaoxindole (**3**).

A solution of **22** (2.6 g, 13.2 mmoles) in ethanol (75 ml) was hydrogenated over Raney nickel (50% in water, 2.6 g) at 3 atmospheres pressure for 4.5 hours. The catalyst was removed by filtration and the solvent was evaporated. The desired product (3-amino-2-chloro-4-pyridyl)acetonitrile (**23**) (680 mg, 31%), a yellow solid, was isolated by chromatography on silica gel eluting sequentially with chloroform and 9:1 chloroform/methanol; ^{1}H nmr (DMSO-d_6): δ 7.62 (d, J = 5.1 Hz, 1 H), 7.17 (d, J = 5.1 Hz, 1 H), 5.66 (br s, 2 H), 3.95 (s, 2 H).

A solution of (3-amino-2-chloro-4-pyridyl)acetonitrile (**23**) (600 mg, 3.6 mmoles) in 6*N* HCl (35 ml) was heated at 100° for 4.5 hours. After cooling, the acid and water were removed *in vacuo*. The residue was dissolved in water and neutralized by addition of solid sodium bicarbonate. The solution was extracted with ethyl acetate and the extract was washed with brine, dried (magnesium sulfate), treated with activated charcoal, and concentrated. The residue was triturated with chloroform and hexane to leave 7-chloro-6-azaoxindole (**3**) as a yellow solid, 280 mg (46%). An analytical sample was prepared by recrystallization from chloroform/hexane, mp 252-254° dec; ^{1}H nmr (DMSO-d_6): δ 10.92 (br s, 1 H), 8.02 (d, J = 5.2 Hz, 1 H), 7.28 (d, J = 5.2 Hz, 1 H), 3.68 (s, 2 H); ir: 1740, 1725, 1705, 1685, 1615, 1570, 1465 cm^{-1}; ms: m/z 170 (64), 168 (100), 142 (38), 140 (73), 139 (60), 105 (92), 78 (64), 51 (73).

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.22. Found: C, 49.69; H, 2.92; N, 16.27.

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[9] Similarly, competitive displacement of the 4-halo substituent occurs during the reactions of dimethyl malonate with 2,4-dichloronitrobenzene and 2,4-difluoronitrobenzene (reference 6). As in these reactions, the products **4a** and **4b** arising from displacement of the chloro substituent *ortho* to the nitro group exhibit a singlet for the malonate methine proton at lower field in the ^{1}H nmr spectrum than the isomeric products **5a** and **5b** arising from displacement of the chloro substituent *para* to the nitro group.

[10] Prepared from 5-chloro-2-hydroxy-3-nitropyridine by a modification of the literature procedure [T. S. Safonova, L. G. Levkovskaya, *Chem. Abstr.*, **70**, 68286y (1969)]. Nitration of 5-chloro-2-hydroxypyridine proved to be cleaner and higher yielding than the literature procedure involving nitration of 2-amino-5-chloropyridine.

[11] Prepared by nitration of 5-fluoro-2-hydroxypyridine followed by reaction of the intermediate (5-fluoro-2-hydroxy-3-nitropyridine) with phosphorus oxychloride/phosphorus pentachloride.

[12] Obtained by the reaction of phosphorus oxychloride/phosphorus pentachloride with 2-hydroxy-3-nitro-5-trifluoromethylpyridine.

[13] Prepared by nitration of 2-hydroxy-6-trifluoromethylpyridine followed by reaction of the intermediate (2-hydroxy-3-nitro-6-trifluoromethylpyridine) with phosphorus oxychloride/phosphorus pentachloride. Separation from the side products, 2-chloro-5-nitro-6-trifluoromethylpyridine and 2-chloro-3,5-dinitro-6-trifluoromethylpyridine was not necessary.

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