

# Polyfluoroaralkylamines: an improved synthesis of 4,5,6,7-tetrafluoroindole

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## Abstract

Tetrafluoroindole (**5**), a precursor for potential biologically-active compounds, was prepared previously in a four-step synthesis from  $C_6F_6$ . However, catalytic reduction of pentafluorophenylacetonitrile (**2**) to 2-pentafluorophenylethyl amine (**3**) is accompanied by a significant amount of a secondary amine, which, like **3**, undergoes cyclization to an indoline and subsequent dehydrogenation to a new indole **8**. The side-reaction in the reduction of **2** to **3** is obviated by the use of  $LiAlH_4/AlCl_3$  (1:1). The final aromatization to yield **5** is vastly improved by replacing  $MnO_2$  with DDQ.

**Keywords:** Polyfluoroaralkylamines; Synthesis; Tetrafluoroindole; NMR spectroscopy; IR spectroscopy

## 1. Introduction

In Previous papers [1–4] we reported the chemistry of polyfluoroaralkylamines, including the synthesis [3] and reactivity [4] of 4,5,6,7-tetrafluoroindole (**5**). This compound and other fluorine-containing amines are of interest as potential bioactive analogs of important biogenic amines of the central nervous system. Compound **5** has been prepared previously by several routes [5–7], while Fujita and Ojima [8] synthesized 3-methyl-4,5,6,7-tetrafluoroindole and explored the related chemistry in detail. During the course of further research with indole **5**, we reviewed all our previous procedures and found several shortcomings in two steps of our original synthesis (Scheme 1) [3], viz. (a) the preparation

of 2-pentafluorophenylethylamine (**3**), which undergoes facile cyclization to indoline **4** and (b) the aromatization of **4** to **5**. We have focused on these steps and report here significant improvements which now provide a reliable and readily achieved synthesis of **5** in four steps from hexafluorobenzene.

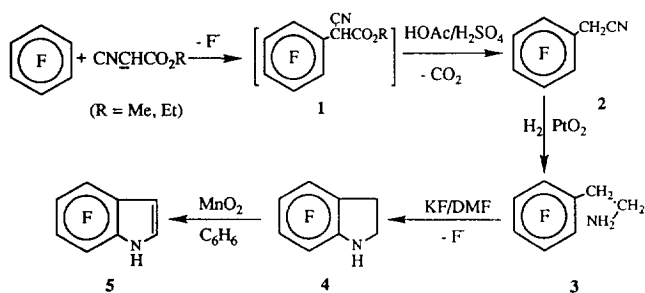
## 2. Results and discussion

### 2.1. 2-Pentafluorophenylethylamine (**3**)

Earlier, we examined several approaches to **3**. All the methods exhibited some undesirable side-reactions or led to unexpected chemistry. Thus, 2-pentafluorophenyl-1-bromoethane reacted with ammonia or potassium phthalimide to give **3**, along with 10%–15% yields of pentafluorostyrene (Scheme 2). Such competing elimination reactions have been observed previously [9], owing to the strong electron-withdrawing effect of the  $C_6F_5$  group and where the nucleophile is also capable of behaving as a moderate base.

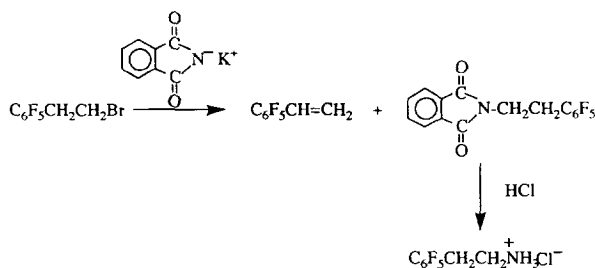
We also attempted to prepare **3** by reaction of  $C_6F_5Li$  with aziridine, by analogy with oxirane. Instead of ring-opening, 4-aziridino-2,3,5,6-tetrafluorobenzene was obtained (Scheme 3).

Our main efforts to prepare **3** were again directed at the reduction of pentafluorophenylacetonitrile (**2**).

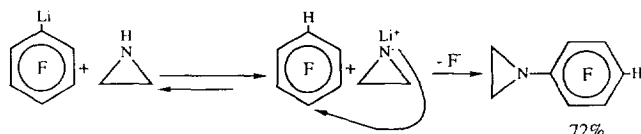


Scheme 1.

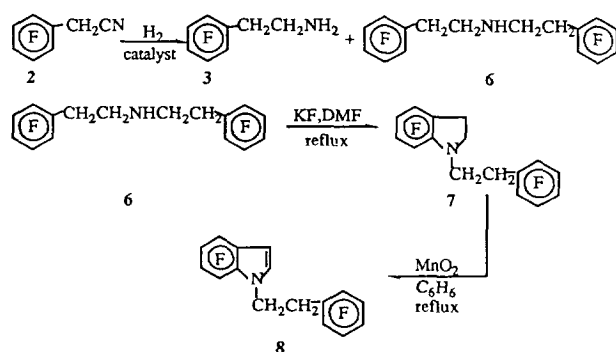
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Scheme 2.



Scheme 3.

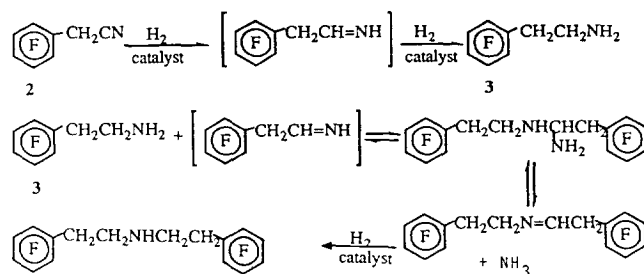


Scheme 4.

The preparation of **2** from  $C_6F_5CH_2Br$  and cyanide ion is accompanied by a 15%–20% yield of a by-product,  $C_6F_5CH_2CH(CN)C_6F_5$  [3,4]. Our approach to **2**, via  $C_6F_6$  and the enolate of alkyl cyanoacetate (Scheme 1), avoids this difficulty and is the method of choice.

The catalytic reduction of **2** proceeded smoothly to give a high yield of amine, isolated as its hydrochloride<sup>1</sup>. However, when the remaining steps in the synthesis of **5** were completed, a significant contaminant, another indole, **8**, was also isolated (Scheme 4). This led us to reassess the reduction of **2**. It is apparent that under the conditions employed, both the desired amine **3** and the secondary amine **6** were formed. When hydrogenation was run with insufficient supply of hydrogen and for an extended time, the side-reaction became predominant. Subsequent cyclization to indolines and aromatization provided the two indoles. The hydrogenation of nitriles to primary amines is complicated by equilibria which lead to secondary amines [10]. While we did not attempt to isolate compound **6**, we suggest the following sequence for its formation (Scheme 5).

<sup>1</sup> The amine should be distilled and used immediately for cyclization to the indoline. It is best to store the amine as its salt in order to minimize intermolecular nucleophilic substitution on the fluorinated ring, which leads to polymers.



Scheme 5.

Table 1

A systematic study of the aromatization of 4,5,6,7-tetrafluorindoline with five aromatization reagents

Aromatization reagent	Temperature (°C)	Time	Yield (%)
Manganese dioxide	80	3–4 d	46–68
Dichlorodicyanobenzoquinone (DDQ)	80	1–2 d	65–68
Potassium (Fremy's salt) nitrosodisulfonate	R.T.	3 d	28
Benzeneseleninic anhydride	R.T.	1 h	–
<i>N</i> -Bromosuccinimide	80	7 h	–

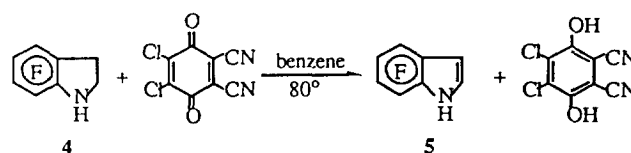
We then investigated the reduction of **2** with the mixed reagent  $LiAlH_4/AlCl_3$  (1:1) [11]. The reaction proceeded rapidly to afford a 75% yield of **3**, with no by-products nor evidence of nucleophilic attack on the polyfluoroaromatic ring, as is often observed with  $LiAlH_4$  alone. This procedure provides the best route to **3**, in two steps from  $C_6F_6$ .

## 2.2. Aromatization of indoline **4** to indole **5**

Fluoride ion-catalyzed cyclization of amine **3** to the indoline **4** proceeded readily. The final step, dehydrogenation of **4** to **5**, catalyzed by freshly prepared activated  $MnO_2$ , gave inconsistent results.

We conducted a systematic study of the aromatization of **4** with five reagents which have been used in related systems, as summarized in Table 1.

DDQ, which is readily available and convenient to use, gave the best results.  $MnO_2$  is not as reliable and is tedious to prepare. The other reagents were less effective or failed to give the indole.



### 3. Experimental details

All infrared spectra were run on a Nicolet 5MX FT-IR spectrometer.  $^1\text{H}$  NMR spectra were obtained using a Varian T-60 analytical spectrometer, with tetramethylsilane as internal or external standard. Elemental analyses were performed at Midwest Microlab, Indianapolis, IN. All melting and boiling points are uncorrected.

#### 3.1. 2-Pentafluorophenylethyl bromide

A mixture of 8.4 g (39.6 mmol) of 2-pentafluorophenylethanol and 7 g of phosphorus tribromide was heated for 24 h at 130 °C in a 100 ml flask equipped with a reflux condenser connected to a gas trap. After adding 40 ml of carbon tetrachloride and 40 ml of water to the cooled reaction mixture, the carbon tetrachloride layer was separated, filtered, dried over anhydrous magnesium sulfate and evaporated in vacuo to give an oil. Fractional distillation gave 8.18 g (75.3%) of 2-pentafluorophenyl-1-bromoethane, b.p. 86–87 °C/12 Torr; lit. values [12] 97–99 °C/25 mmHg.  $^1\text{H}$  NMR (neat)  $\delta$ : 3.58 (m, 4,  $\text{CH}_2$ ) ppm.

#### 3.2. N-2-Pentafluorophenylethyl phthalimide

2-Pentafluorophenylethyl bromide (43.60 g, 0.159 mol) and 29.6 g (0.160 mol) of potassium phthalimide were combined in a 250 ml two-necked flask fitted with a mechanical stirrer and reflux condenser. The mixture was heated for 12 h with stirring at 180–190 °C using an oil bath. After cooling the mixture, the condenser was placed in a downward position and the liquid distilled in vacuo. Fraction 1 (3.2 g) distilled at 60 °C/24 Torr. It was identified by  $^1\text{H}$  NMR and IR spectroscopies as pentafluorostyrene. IR (neat) ( $\text{cm}^{-1}$ ): 3100, 3010, 2940, 2920 (s, CH); 1650, 1620, 1580, 1500, 1480 (aromatic); 1500, 1140 (vs, CF); 950–920 (s,  $\text{CH}=\text{CH}_2$ ).  $^1\text{H}$  NMR (neat)  $\delta$ : 6.21 (broad complex multiplet) ppm.

To the semisolid remaining in the flask was added 75 ml of 95% ethanol and the mixture refluxed for 1.5 h. The mixture was filtered on a Büchner funnel and the solid hydrolyzed by refluxing in a solution consisting of 25 ml conc. HCl and 75 ml  $\text{H}_2\text{O}$  contained in a 250 ml two-necked flask fitted with a mechanical stirrer and condenser.

After the mixture was allowed to cool and made basic with sodium carbonate, it was extracted with several portions of ether. The combined ethereal extracts were washed with water and dried over anhydrous  $\text{MgSO}_4$ . Concentration in vacuo left a yellow oil. The yield was 84%.  $^1\text{H}$  NMR and IR spectroscopies indicated the presence of the desired amine and phthalimide group. IR (neat) ( $\text{cm}^{-1}$ ): 3540–3000 (s, b); 2980, 2920,

2860 (s, b,  $\text{CH}_2$ ); 1730 (w,  $\text{C}=\text{O}$ ); 1650, 1540, 1450 (aromatic); 1500, 1080 (s, CF).  $^1\text{H}$  NMR ( $\text{CCl}_4$ )  $\delta$ : 7.78 (m, phenyl  $H$ ); 4.8 (m,  $\text{NH}$ ); 3.8 (m); 1.8 (m); 1.2 (m,  $\text{CH}_2\text{CH}_2$ ) ppm.

#### 3.3. *p*-Aziridinotetrafluorobenzene (nc) <sup>2</sup>

A 500 ml three-necked flask was equipped with a mechanical stirrer, a condenser carrying a calcium chloride drying tube at the top and a three-necked Claisen adapter. One of the necks was equipped with a 500 ml pressure-equilibrating dropping funnel connected to a nitrogen supply, another was fitted with a rubber septum and the third connected to a 50 ml pressure-equilibrating dropping funnel. The reaction flask was cooled at –78 °C and charged through the septum with 132 ml of 1.6 M *n*-butyl-lithium in hexane (0.21 M). To this cold solution was added slowly, drop by drop, 34.86 g (0.21 mol) of pentafluorobenzene dissolved in 300 ml of ether. Two hours after addition had been completed, 18.06 g (0.42 mol) of freshly distilled aziridine was slowly added dropwise from the 50 ml dropping funnel over a period of 10 min. The solution turned pink. The Dry Ice/acetone bath was replaced with  $\text{CCl}_4$ /Dry Ice bath (–26 °C) and the mixture allowed to stir for 10 h without replenishing the bath. After acidification with 100 ml of 4 N HCl, the yellow acidified solution was extracted with several portions of ether, the ether washed with water and dried over anhydrous  $\text{MgSO}_4$ . The ether was removed by distillation. Two fractions, b.p. 54–57 °C/760 Torr and 60–77 °C/760 Torr, respectively contained a mixture of ether and aziridine as identified by  $^1\text{H}$  NMR spectroscopy. A colorless liquid (32.8 g) was collected at 74 °C/12 Torr. This product was identified as *p*-aziridinotetrafluorobenzene, 72% yield. (Analysis: Calc. for  $\text{C}_8\text{H}_5\text{NF}_4$ : C, 50.28; H, 2.58; N, 7.33%. Found: C, 50.71; H, 2.24; N, 7.40%.) IR (neat) ( $\text{cm}^{-1}$ ): 3030, 2950 (vs, CH); 1630, 1580, 1500, 1480 (vs, aromatic); 1040 (vs, CF).  $^1\text{H}$  NMR (neat)  $\delta$ : 2.2 (m, 4,  $\text{CH}_2\text{CH}_2$ ); 6.7 (m, 1,  $\text{C}_6\text{F}_4\text{H}$ ) ppm.

#### 3.4. (Pentafluorophenyl)acetonitrile (2)

This compound was prepared according to a previously described procedure [13].

#### 3.5. 2-Pentafluorophenylethylamine by catalytic hydrogenation

##### (A) 2-Pentafluorophenylethylamine hydrochloride

To a solution of 27.8 g (0.134 mol) of (pentafluorophenyl)acetonitrile in 150 ml of absolute ethanol and

<sup>2</sup> This compound was obtained in an attempt to prepare 2-pentafluorophenylethylamine (3).

70 ml of water containing 17 ml of concentrated hydrochloric acid, was added 0.25 mg of platinum dioxide catalyst. The mixture was shaken in a Parr shaker with hydrogen at 3 atm and room temperature. After reduction was complete, the solvent was removed in vacuo, followed by filtration on a Büchner funnel and the solid washed thoroughly with anhydrous acetone. White crystals were obtained, m.p. 275–278 °C. Addition of acetone to the filtrate caused precipitation of additional hydrochloride. The combined mass of crystals was 22 g (69% yield). Recrystallization of a small amount of the crude product gave white crystals, m.p. 279–280 °C. IR (KBr disk) ( $\text{cm}^{-1}$ ): 3000, 2900 (s, CH); 1650, 1610 (s, aromatic); 1500, 1100 (s, CF).

(B) 2-Pentafluorophenylethylamine (3)

A chilled solution of 2-pentafluorophenylethylamine hydrochloride in 150 ml of water was transferred to a separating funnel, and a small amount of solid sodium carbonate and 10 ml of diethyl ether added alternately. The mixture was shaken and kept cool by the addition of a small amount of crushed ice. The process was continued until the water layer was distinctly alkaline. The ether layer was separated and the water layer extracted exhaustively with small volumes of ether. The combined ether solution was washed with 20 ml of water and dried over anhydrous magnesium sulfate. The ether was removed in vacuo when 12 g (63% yield) of yellowish residue was obtained, which was used without further purification for the preparation of 4,5,6,7-tetrafluoroindoline (4).

An analytical sample was obtained by distilling 4.0 g of the crude product in a microvacuum-jacketed distillation apparatus. A colorless liquid (3.0 g) having a very strong ammoniacal odor was collected at 80–84 °C/20 Torr.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (s, 2H,  $\text{NH}_2$ ); 2.88 (s, 4H,  $\text{CH}_2$ ) ppm. IR (hexachlorobutadiene mull) ( $\text{cm}^{-1}$ ): 3400, 3340 (s,  $\text{NH}_2$ ); 2920, 2840 (s,  $\text{CH}_2$ ); 1650, 1540, 1500 (s, aromatic); 1440, 1150 (s, CF).

(C) 2-Pentafluorophenylethylamine (3) by  $\text{LiAlH}_4/\text{AlCl}_3$  reduction

An adaptation of Nystrom's method [11] was employed. A 250 ml, three-necked flask was equipped with a reflux condenser, a mechanical stirrer and an addition funnel. The reaction was conducted in a nitrogen atmosphere. Lithium aluminum hydride solution in ether (1 M, 24 ml, 0.024 mol) was placed in the flask. Through the addition funnel, a solution of 3.1 g (0.024 mol) of anhydrous aluminum chloride in 15 ml of dry ether was added rapidly to the hydride solution. After 5 min, a solution of 5 g (0.024 mol) of (pentafluorophenyl)acetonitrile in 15 ml of dry ether was added dropwise to the well-stirred mixture. One hour after addition was complete, water was added dropwise to decompose excess hydride, followed by 40 ml of 6 N sulfuric acid and 20 ml of water. The clear mixture

was transferred to a separating funnel, and after separating the ether layer, the aqueous layer was extracted with four 25 ml portions of ether. The aqueous layer was cooled in an ice/water bath while potassium hydroxide pellets were added continuously until the pH of the solution was 11. The alkaline mixture was diluted with 100 ml of water and then extracted with four 25 ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed to give 0.5 g of crude material from the acidic extract and 3.7 g (73% yield) of crude compound 3 from the basic extract. The analytical sample was obtained by fractional distillation through a 25 cm column under reduced pressure to give 2-pentafluorophenylethylamine (3), b.p. 81–84 °C/20 Torr. The NMR and IR spectra were identical to that of compound 3 obtained by catalytic hydrogenation.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.50 (s, 2H,  $\text{NH}_2$ ); 2.88 (s, 4H,  $\text{CH}_2$ ) ppm.  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$ : 2.08 (s, 1H,  $\text{NH}_2$ ); 2.72 (s, 2H,  $\text{CH}_2$ ); 2.80 (s, 2H,  $\text{CH}_2$ ) ppm.

3.6. 4,5,6,7-Tetrafluoroindoline (4)

To a 500 ml three-neck flask equipped with a mechanical stirrer, a reflux condenser and an addition funnel, was added 12 g (0.0057 mol) of 2-pentafluorophenylethylamine (3), a yellow oil, in 300 ml of anhydrous dimethylformamide (DMF), obtained by stirring technical-grade dimethylformamide over anhydrous cupric sulfate, then filtering and distilling under reduced pressure. Anhydrous potassium fluoride (6 g) was added and the mixture heated under reflux with mechanical stirring in an atmosphere of dry nitrogen for 4 h. After cooling to room temperature, most of the DMF was removed by vacuum distillation. The residue was transferred to a steam-distillation apparatus and steam-distilled exhaustively. Tetrafluoroindoline (4) (6.8 g), white crystals, was obtained (61% yield), m.p. 58–68 °C. The odoriferous compound 4 was further purified by sublimation in vacuo.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.13 (t, 2H,  $\beta\text{-CH}_2$ ); 3.65 (complex, 3H,  $\alpha\text{-CH}_2$  and NH) ppm. IR (KBr disk) ( $\text{cm}^{-1}$ ): 3400 (m, NH); 2940, 2864 (m, CH); 1640, 1517 (s, aromatic); 1500, 1100 (s, CF).

3.7. 1-(2'-Pentafluorophenylethyl)-4,5,6,7-tetrafluoroindoline (7)

(A) Bis(pentafluorophenylethyl)amine (6)

The by-product 6 was obtained from the catalytic hydrogenation to form 2-pentafluorophenylethylamine (3). The reaction was run under similar conditions except at lower hydrogen pressure and longer reaction time. To a solution of 27.8 g (0.134 mol) of (pentafluorophenyl)acetonitrile (2) in 150 ml of absolute ethanol and 70 ml of water containing 17 ml of concentrated hydrochloric acid, was added 0.25 mg of

platinum dioxide catalyst. The mixture was shaken in a Parr shaker with hydrogen at 1–3 atm pressure and room temperature. After reduction was complete, the solvent was removed in vacuo, followed by filtration on a Büchner funnel and washed thoroughly with anhydrous acetone. The white crystals obtained were added to 150 ml of ice/water in a separating funnel. To the chilled mixture, a small amount of solid sodium carbonate and 10 ml of diethyl ether were added alternately. The mixture was shaken and kept cool by the addition of a small amount of crushed ice. The process was continued until the water layer was distinctly alkaline. The ether layer was separated and the water layer extracted exhaustively with small volumes of ether. The combined ether solution was washed with 20 ml of water and dried over anhydrous magnesium sulfate. The ether was removed in vacuo when a yellowish residue was obtained. TLC showed the existence of compound **6** and 2-pentafluorophenylethylamine (**3**). No effort was made to separate by-product **6**. The mixture was cyclized to obtain compound **4** and the by-product **7**.

(B) 1-(2'-Pentafluorophenylethyl)-4,5,6,7-tetrafluoroindoline (**7**)

The reaction was conducted under the same conditions as used for the preparation of 4,5,6,7-tetrafluoroindoline (**4**). After steam-distillation, only 2.1 g of 4,5,6,7-tetrafluoroindoline (**4**) was collected. Water was removed from the residue by distillation when about 4 g of a yellowish solid was obtained. The NMR spectrum showed that it was compound **7**, i.e. 1-(2'-pentafluorophenylethyl)-4,5,6,7-tetrafluoroindoline. No effort was made to purify by-product **7**.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.13 ( $\beta\text{-CH}_2$ ); 3.18 ( $\text{CH}_2$ ); 3.50 ( $\text{N-CH}_2$ ); 3.65 ( $\alpha\text{-CH}_2$ ) ppm.

3.8. 4,5,6,7-Tetrafluoroindole (**5**) by activated manganese dioxide aromatization

(A) Activated manganese dioxide

Activated manganese dioxide was prepared according to Attenburrow's procedure [14]. A solution of manganese sulfate tetrahydrate (1110 g) in water (1500 ml) and a solution of sodium hydroxide (40%, 1170 ml) were added simultaneously during 1 h to a hot stirred solution of potassium permanganate (960 g) in water (6 l). Manganese dioxide precipitated as a fine brown solid. Stirring was continued for an additional hour and the solid was then filtered and washed with water until the washings were colorless. The solid was dried in an oven at 100–120 °C and ground to a fine powder before use.

(B) 1-(2'-Pentafluorophenylethyl)-4,5,6,7-tetrafluoroindole (**8**) (nc)

A mixture (42.3 g) containing 4,5,6,7-tetrafluoroindoline (**4**) and 1-(2'-pentafluorophenylethyl)-4,5,6,7-

tetrafluoroindoline (**7**) was placed in a 1 l one-neck flask equipped with a mechanical stirrer and 500 ml of benzene, which had been predried over sodium, was added. Then, 20 g of Linde-type 4X molecular sieves and 30 g (0.35 mol) of activated manganese dioxide were added. The mixture was stirred at room temperature for 60 h. After the mixture had been filtered on a Büchner funnel using Celite, the solid residue was transferred to a Soxhlet apparatus and extracted with 500 ml of dry benzene for 8 h. The filtrate and extracts were combined and the benzene removed on a rotary evaporator to give 27 g of a brownish solid. The NMR spectrum of the crude product showed that about one-third of the starting material had been aromatized to the 4,5,6,7-tetrafluoroindole (**5**). The crude product was placed in a 1 l, one-neck flask and treated with an additional 30 g of activated manganese dioxide in 500 ml of dry benzene for 2 d under similar conditions. After filtration and removal of solvent, 19.2 g of a white solid, m.p. 128–131 °C, were obtained.

TLC analysis showed that it was a mixture of two compounds. To separate the mixture, 3 g of the crude product was dissolved in 3 ml of benzene and transferred to a 3 ft  $\times$  2 cm chromatography column packed with 100 g of neutral alumina in practical grade hexane, and eluted first with hexane (350 ml), then 70:30 hexane/diethyl ether (350 ml), 50:50 hexane/diethyl ether (350 ml) and, finally, diethyl ether (350 ml). The solvent was removed to give 0.7 g of 4,5,6,7-tetrafluoroindole (**5**), m.p. 89–91 °C, and 1.5 g (50%) of 1-(2'-pentafluorophenylethyl)-4,5,6,7-tetrafluoroindole (**8**) as white crystals, m.p. 139–140 °C. (Analysis: Calc. for  $\text{C}_{16}\text{H}_6\text{F}_9\text{N}$ : C, 50.13; H, 1.57; N, 3.66%. Found: C, 50.02; H, 1.52; N, 4.03%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 3.38 (t, 2H,  $\text{CH}_2$ ); 4.60 (t, 2H,  $\text{N-CH}_2$ ); 6.64 (d, 1H,  $\alpha\text{-CH}$ ); 6.92 (d, 1H,  $\beta\text{-CH}$ ) ppm. IR (KBr disk) ( $\text{cm}^{-1}$ ): 2950 (w, aliphatic); 1630, 1540, 810, 760, 720 (s, aromatic); 1360, 1260, 1180, 1120, 1080 (m, CF).

Tetrafluoroindole (**5**) was sublimed at 60 °C/1–2 Torr to give white crystals, m.p. 91–92 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ : 8.37 (s, broad, 1H, NH); 7.17 (1H,  $\beta\text{-CH}$ ); 6.76 (1H,  $\alpha\text{-CH}$ ) ppm. IR (KBr disk) ( $\text{cm}^{-1}$ ): 3420 (s, NH); 3100 (s, CH); 1660, 1600, 1540, 1500 (s, aromatic); 1490, 1130, 1000 (s, CF).

3.9. 4,5,6,7-Tetrafluoroindole (**5**) by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) aromatization

To a 50 ml two-neck flask, equipped with a reflux condenser, an addition funnel and a magnetic stirrer, were added 257 mg (0.00157 mol) of the quinone and 7 ml of predried benzene. A dark green solution was obtained. 4,5,6,7-Tetrafluoroindoline (**4**) (300 mg, 0.00157 mol) was added to the solution and the mixture heated under reflux under nitrogen for 2 d. After the reaction mixture had been cooled to room temperature,

it was diluted with 10 ml of petroleum ether. The mixture was filtered and the filtrate washed thoroughly with petroleum ether. The solvent was allowed to evaporate and the residue passed through a 2 ft×1 cm chromatography column packed with 10 g of neutral alumina in practical grade hexane, and eluted first with hexane (100 ml), then 70:30 hexane/diethyl ether (100 ml), 50:50 hexane/diethyl ether (100 ml) and, finally, diethyl ether (100 ml). The solvent was removed to yield 200 mg (68%) of 4,5,6,7-tetrafluoroindole (**5**), m.p. 89–91 °C. The NMR spectrum and TLC were identical to those of compound **5** obtained from the activated manganese dioxide aromatization.

### 3.10. 4,5,6,7-Tetrafluoroindole (**5**) by potassium nitrosodisulfonate (Fremy's salt) aromatization

A modification of the method used by Wehrli and Schaer [15] was employed. Fremy's salt (900 mg, 0.00262 mol) was dissolved in 50 ml of ice-cold 4% sodium carbonate solution and placed in a one-neck, round-bottom flask. 4,5,6,7-Tetrafluoroindoline (**4**) (250 mg, 0.00131 mol) was added and the mixture stirred at room temperature for 3 d. The reaction mixture was extracted with four 30 ml portions of ether and the combined ether layers washed with saturated sodium chloride solution, then water, and dried over anhydrous magnesium sulfate. After the solvent had been removed on a rotary evaporator, the residue was passed through a 2 ft×1 cm chromatography column packed with 10 g of neutral alumina in practical grade hexane, and eluted first with hexane (100 ml), then 70:30 hexane/

diethyl ether (100 ml), 50:50 hexane/diethyl ether (100 ml) and, finally, diethyl ether (100 ml). The solvent was removed to give 70 mg (28%) of 4,5,6,7-tetrafluoroindole (**5**), m.p. 89–91 °C. The NMR spectrum and TLC were identical to those of 4,5,6,7-tetrafluoroindole (**5**) obtained from the activated manganese dioxide aromatization.

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