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SYNTHESIS OF 1-(PENTAFLUOROPHENYL)-β-CARBOLINE

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SUMMARY

Thermal condensation of tryptamine with pentafluorobenzaldehyde in ethanol afforded 1-(pentafluorophenyl)-1,2,3,4-tetrahydro-β-carboline (**I**, 51% yield), together with two by-products (**IIa**, 9% yield and **IIb**, 14% yield) which were produced by nucleophilic substitution of an aromatic fluorine atom by the tryptamine amino group. In solvent acetic acid, the same reactants gave 2-acetyl-1-(pentafluorophenyl)-1,2,3,4-tetrahydro-β-carboline (**III**, 64% yield) as the main product, together with a reduced yield (20%) of **I**. Dehydrogenation of **I** with selenium dioxide provided 1-(pentafluorophenyl)-β-carboline (**IV**) in 84% yield; **III** also gave **IV** in 72% yield. Partial dehydrogenation of **I** with potassium permanganate provided 1-(pentafluorophenyl)-3,4-dihydro-β-carboline (**V**, 80% yield) but **V** could not be obtained from **III**. Indole itself provided (pentafluorophenyl)bis(3-indolyl)methane (**VI**, 82% yield) by simple reflux with pentafluorobenzaldehyde in propanol. In solvent acetic acid, the yield of **VI** was 78%.

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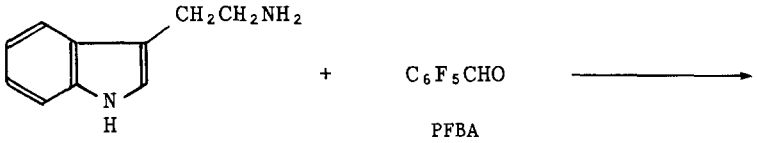
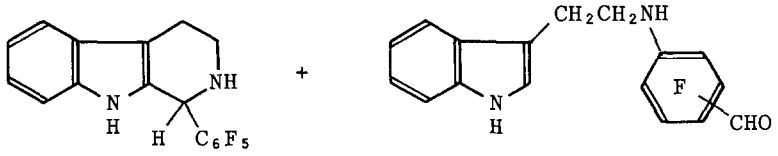
INTRODUCTION

Two essential amino acids, tryptophan and histidine, contain indole and imidazole rings, respectively, and derivatives of these ring systems occur widely in both plant and animal metabolites. Therefore, introduction of fluorinated groups into these ring systems has been considered as a basis for potential drugs or agricultural chemicals. We have recently described the facile thermal condensation of imidazoles [1] and indoles [2] with trifluoroacetaldehyde, and we have applied the condensation to the syntheses of several biologically interesting heterocyclic compounds having trifluoromethyl groups [3,4]. In addition to the trifluoromethyl group, pentafluorophenyl is an attractive substituent for us, and the condensation has now been extended to pentafluorobenzaldehyde (PFBA). However, PFBA showed behavior different from that of trifluoroacetaldehyde. The reaction with imidazole resulted in no condensation but in nucleophilic substitution of an aromatic fluorine atom of PFBA by an imidazole ring nitrogen [5]. In this paper, we describe the condensation of indoles with PFBA.

RESULTS AND DISCUSSION

In a manner similar to that of trifluoroacetaldehyde [4], PFBA condensed with tryptamine by simple reflux in ethanol, and provided 1-(pentafluorophenyl)-1,2,3,4-tetrahydro-β-carboline (**I**) in 50.6% yield. The condensation, however, was accompanied by nucleophilic substitution of an aromatic fluorine of PFBA by the side-chain amino group of tryptamine. The by-products consisted of two regioisomers, **IIa** ortho and **IIb** para, in yields of 8.6% and 13.7%, respectively. Careful silica gel chromatography permitted separation of the three products, which were characterized by high-resolution mass, mass and NMR spectra. The mass spectrum of **I** shows a fragmentation pattern typical of 1-substituted 1,2,3,4-tetrahydro-β-carbolines [4,6]: large ion peaks at 338 (M^+), 171 ($M^+ - C_6F_5$), and 309 ($M^+ - CH_2NH$). The last ion is generated via a retro-Diels-Alder





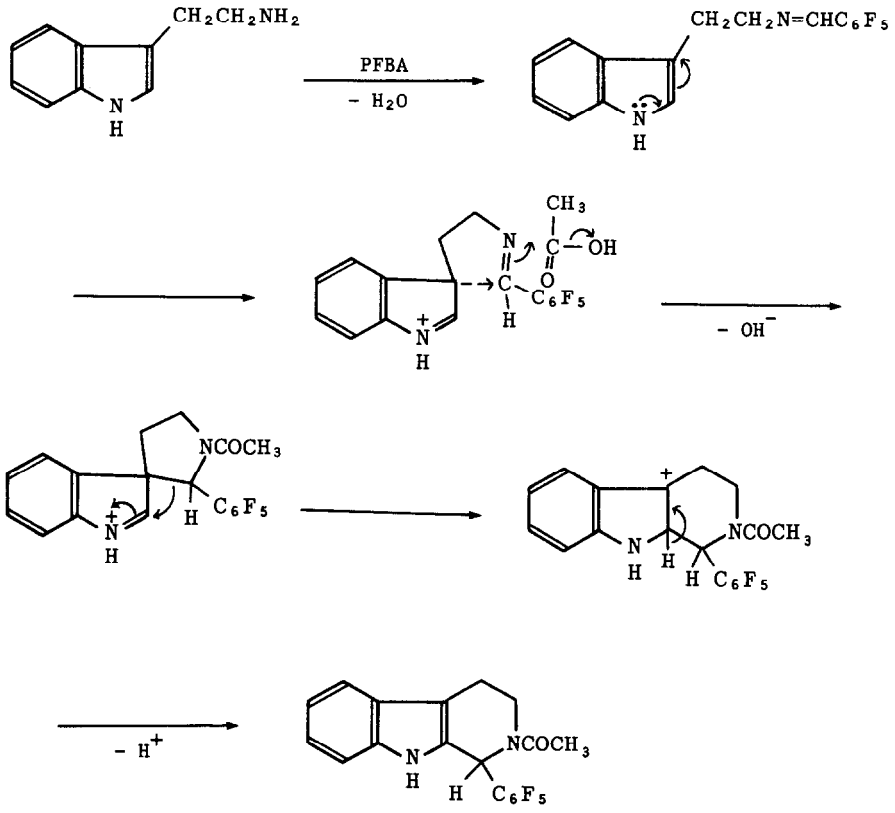
I **IIa,b**

a) ortho-CHO b) para-CHO

fragmentation of the tetrahydropyridine ring. In contrast to that of **I**, mass spectra of **IIa** and **IIb** show a smaller molecular ion peak at 336 and the largest peak at 130, the indolylmethyl cation characteristic of 3-alkylindoles. ^{19}F NMR spectra of the products show multiplets which were analyzed by computer. The pentafluorophenyl group of I appears as three groups of signals at - 0.5, 14.6, and 21.2 ppm in the ratio of 1:2:2. Four distinct peaks are found for **IIa** at - 13.7, 3.9, 12.3, and 15.9 ppm with equal intensities. The chemical shifts and coupling constants are consistent with the structures of ortho substituted tetrafluorobenzenes. On the other hand, **IIb** shows two fluorine peaks of equal intensity at 0.6 and 14.6 ppm, indicating para substitution.

Nucleophilic substitution reactions of polyfluorinated aromatic compounds with amines are known [7], and electron-withdrawing groups such as formyl should enhance the reactivity of ortho and para fluorines. In order to avoid such nucleophilic substitution and extended chromatography, the condensation was carried out under acidic conditions. Addition of hydrochloric acid to the ethanol medium prevented the formation of **I** and only tarry matter was obtained. While the condensation proceeded successfully in solvent acetic acid, acetylation at the 2-position of **I** also occurred and **III** was

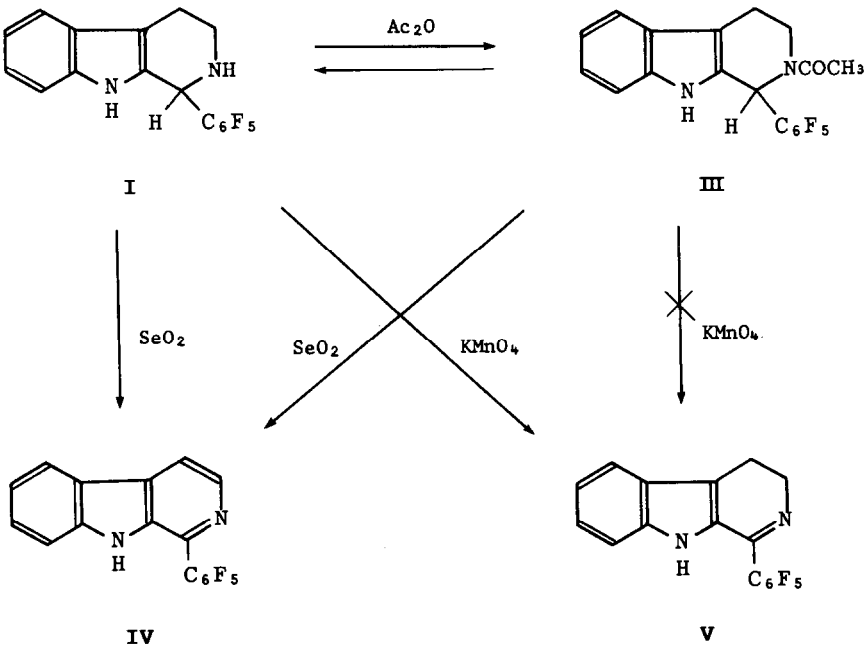
obtained as the main product in 63.7% yield, together with a reduced yield (20.4%) of I. Since I could not be acetylated by refluxing acetic acid, the acetylation may have occurred during condensation by the following pathway:



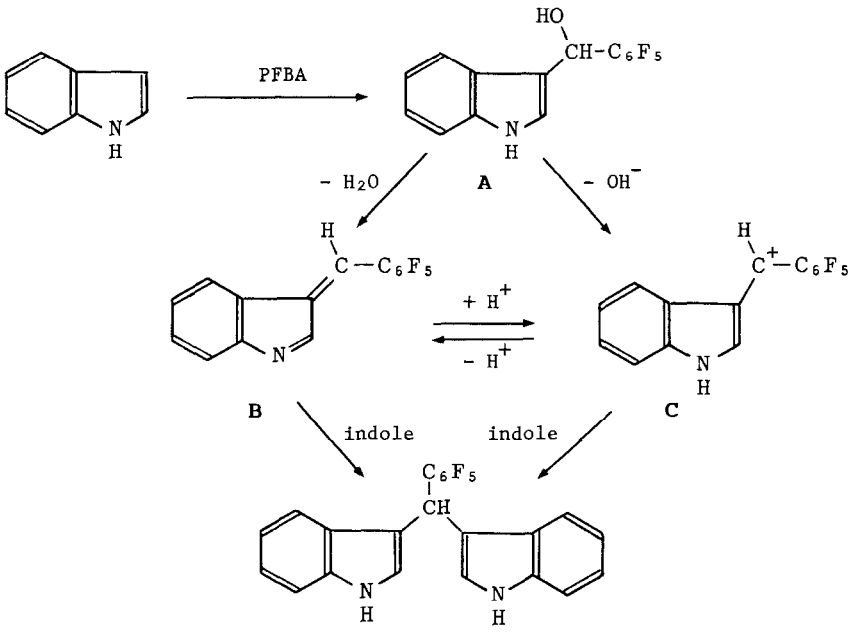
III

The acetylation of I with acetic anhydride gave III quantitatively (refluxing in acetic acid for 5 hours). Hydrolysis of III to I was difficult: no reaction occurred under acidic conditions (heating at 100 °C for 5 hours in 3N hydrochloric acid and cosolvent ethanol), while fluorine substitution occurred under basic conditions. Fortunately, the desired

1-(pentafluorophenyl)-β-carboline (**IV**) could be synthesized directly by the reaction of **III** with selenium dioxide (71.5% yield); apparently deacetylation occurs during or after the dehydrogenation sequence. Dehydrogenation of **I** with selenium dioxide also provided **IV** in 83.8% yield. Partial dehydrogenation of **I** with potassium permanganate at 0°C in acetone gave 1-(pentafluorophenyl)-3,4-dihydro-β-carboline (**V**) in 80% yield. In the case of the trifluoromethyl analogs, partial dehydrogenation proved more difficult [4]; probably, conjugation with the pentafluorophenyl group contributes to facilitate elimination of the hydrogens at the 1 and 2 positions of **I** [8]. In contrast to **I**, **III** does not dehydrogenate with potassium permanganate under the same reaction conditions; at higher temperature, a mixture of **IV** and unchanged **III** was obtained. Thus, **III** is a good intermediate for **IV**, but not for **V**.



Under neutral or acidic conditions, indole itself condensed with PFBA. Simple reflux of two molar equivalents of indole with PFBA in propanol afforded (pentafluorophenyl)bis(3-indolyl)methane (**VI**) in 82.0% yield together with unreacted indole (15.8% recovery). Similar reflux in acetic acid afforded **VI**



VI

in 78.1% yield without recovery of indole. In contrast to the condensation of indole with trifluoroacetaldehyde [2], no 1:1 adduct (**A**) was obtained. Under the adopted reaction conditions, **A** apparently eliminates water to form the methyleneindolenine (**B**) and another molecule of indole adds to **B**. Under acidic conditions, loss of the hydroxyl group from **A** or protonation of **B** would lead to a carbocation (**C**) which may attack indole. While the trifluoromethyl group destabilizes the carbocation [9], the pentafluorophenyl group does not [8]. Therefore, PFBA behaves like other carbonyl compounds in the condensation with indoles [10]. The condensation of substituted indoles with PFBA has been used for the preparation of possible psychopharmacological agents [11].

EXPERIMENTAL

Pentafluorobenzaldehyde (PFBA) was obtained from Yarsley Technical Centre and was distilled under argon prior to use. Analytical methods and instrumentation have been described previously [4]. ^{1}H and ^{19}F NMR were recorded on a Hitachi R-90H FT spectrometer (90 MHz, TMS as internal reference for ^{1}H, and 84.68 MHz, hexafluorobenzene as internal reference for ^{19}F) in acetone-d_6 unless otherwise noted. ^{19}F NMR spectra are reported with positive δ values down field from the reference. Elemental analyses are not given for all compounds because complete combustion could not be achieved, even in the presence of vanadium oxide; however, identity and homogeneity are supported by millimass data, NMR spectra and chromatographic behavior.

Condensation of tryptamine with PFBA in ethanol

To a solution of tryptamine (1.60g, 10 mmol) in ethanol (20 ml), PFBA (1.96g, 10 mmol) was added slowly and the solution was heated at reflux for 24 hours under argon. The solvent and water were removed by evaporation and the residual material, dissolved in the minimum volume of dichloromethane, was applied to a column of silica gel (100ml, 200mesh) and the column was eluted with ‹1› dichloromethane and ‹2› ether-dichloromethane 1:1. The mixture of products was resolved into three fractions: the fastest moving material was eluted with solvent ‹1› and consisted of 0.29g (8.9% yield) of Nα-(2'-formyl-3',4',5',6'-tetrafluorophenyl)tryptamine (IIa): mp. 172~173 °C; yellow grains from ethanol; MS m/e (relative intensity) 336 (18) M^+, 206 (7), 130 (100) C_9H_8N; ^{1}H NMR δ 3.08 (t, 2, J = 7Hz, α-CH_2), 3.83 (m, 2, β-CH_2), 7.22 (d, 1, 2-H), 7.01, 7.09, 7.37, 7.56 (m, 4, 4~7-H), 8.7 (broad s, 1, NH), 10.06 (s, 1, CHO); ^{19}F NMR δ 12.3 (m, 1, J = 21Hz and 7Hz, 3-F), - 13.7 (t, 1, J = 21Hz, 4-F), 15.9 (t, 1, J = 21Hz, 5-F), 3.9 (m, 1, J = 21Hz, 6-F); Milli-MS Found M^+ 336.0857, Calcd. as $C_{17}H_{12}F_4N_2O$ 336.0884. The second fraction was eluted with solvent system ‹2› and consisted of 0.46g (13.7% yield) of Nα-(4'-formyl-2',3',5',6'-tetrafluorophenyl)tryptamine (IIb): mp. 106~108 °C; colorless grains from ethanol; MS m/e (relative intensity) 336

(20) M^+, 206 (3), 130 (100) C_9H_8N; ^1H NMR δ 3.13 (t, 2, J = 7Hz, β-CH_2), 3.87 (t-d, 2, J = 7Hz, α-CH_2), 7.20 (d, 1, J = 2Hz, 2-H), 7.01, 7.09, 7.38, 7.58 (m, 4, 4∿7-H), 10.02 (s, 1, CHO); ^{19}F NMR δ 0.6 (d, 2, J = 12Hz, 2,6-F), 14.6 (d, 2, J = 12Hz, 3,5-F); Milli-MS Found M^+ 336.0838, Calcd. as $C_{17}H_{12}F_4N_2O$ 336.0884. The last fraction was eluted with solvent system <2> and consisted of 2.12g (62.7% yield) of 1-(pentafluorophenyl)-1,2,3,4-tetrahydro-β-carboline (I): mp. 157∿159°C; colorless needles from ethanol; MS m/e (relative intensity) 338 (100) M^+, 337 (25) M^+ - H, 309 (75) M^+ - CH_2NH, 290 (39), 289 (44), 171 (62) M^+ - C_6F_5; ^1H NMR δ 2.82 (m, 2, 4-H), 3.26 (m, 2, 3-H), 5.70 (s, 1, 1-H), 7.00, 7.04, 7.22, 7.46 (m, 4, 5∿8-H); ^{19}F NMR δ 21.2 (d-d, 2, J = 21Hz and 7Hz, 2,6-F), - 0.5 (t-d, 2, J = 21Hz and 7Hz, 3,5-F), 6.2 (t, 1, J = 21Hz, 4-F); Milli-MS Found M^+ 338.0898, Calcd. as $C_{17}H_{11}F_5N_2$ 338.0842.

Condensation of tryptamine with PFBA in acetic acid

To a suspension of tryptamine (8.01g, 50 mmol) in acetic acid (100 ml), was added PFBA (9.80g, 50 mmol) and the suspension was heated at reflux for 24 hours under argon. The mixture became homogeneous with the rise in temperature. The solvent and water were removed by evaporation, and the residual solid was recrystallized from ethanol to give 9.55g of 2-acetyl-1-(pentafluorophenyl)-1,2,3,4-tetrahydro-β-carboline (III): mp. 253∿254°C; colorless grains from ethanol; MS m/e (relative intensity) 380 (100) M^+, 337 (28) M^+ - $COCH_3$, 321 (23), 318 (29), 290 (21), 289 (27), 213 (15), 171 (43), 144 (32); ^1H NMR δ 2.21 (s, 3, $COCH_3$), 6.85 (s, 1, 1-H), 2.98 (m, 2, 3-H), 2.84 (m, 2, 4-H), 7.03, 7.08, 7.26, 7.51 (m, 4, 5∿8-H); ^{19}F NMR δ 23.3 (d-d, 2, J = 21Hz and 7Hz, 2,6-F), 0.0 (t-d, 2, J = 21Hz and 7Hz, 3,5-F), 6.5 (t, 1, J = 21Hz, 4-F); Milli-MS Found M^+ 380.0943, Calcd. as $C_{19}H_{13}F_5N_2O$ 380.0946. The mother liquor was evaporated to dryness and the residual material was fractionated on a silica gel column (180 ml, eluants <1> ether-dichloromethane 1:20 and <2> ether-dichloromethane 1:1). Solvent <1> provided an additional 2.56g (63.7% total yield) of III and solvent <2> gave 3.45g (20.4% yield) of I.

Dehydrogenation of I with potassium permanganate

To a solution of I (0.34g, 1 mmol) in acetone (40 ml), was added powdered potassium permanganate (0.16g, 1 mmol) in small portions at 0 °C, and the solution was stirred for 5 hours. A brown precipitate was filtered off and the filtrate was evaporated to dryness. The residual material was purified on a silica gel column (100 ml, eluted with ether-dichloromethane 1:9) and recrystallization from chloroform gave 0.27g (80% yield) of 1-pentafluorophenyl-3,4-dihydro-β-carboline (V) as pale yellow grains: mp. 178 ∿180°C; MS m/e (relative intensity) 336 (96) M^+, 335 (100) M^+ - H, 308 (15), 289 (17), 288 (11); ^1H NMR δ 4.10 (d-d, 2, J = 10Hz and 8Hz, 3-H), 2.99 (d-d, 2, J = 10Hz and 8Hz, 4-H), 7.55, 7.68, 7.81, 8.10 (m, 4, 5∿8-H); ^{19}F NMR δ 21.4 (d-d, 2, J = 22Hz and 8Hz, 2,6-F), 0.8 (t-d, 2, J = 22Hz and 8Hz, 3,5-F), 8.2 (t, 1, J = 21Hz, 4-F); Milli-MS Found M^+ 336.0663, Calcd. as $C_{17}H_9F_5N_2$ 336.0684.

Dehydrogenation of I with selenium dioxide

To a suspension of I (3.38g, 10 mmol) in acetic acid (150 ml), selenium dioxide (2.22g, 20 mmol) was added and the mixture was heated at reflux for 5 hours. The reaction mixture was cooled, a black solid was filtered off and the filtrate was evaporated to dryness. The residual material was applied to a silica gel column (100 ml) and was eluted with ether-dichloromethane 1:9. There was obtained 2.80g (83.8% yield) of 1-(pentafluorophenyl)-β-carboline (IV): mp. 228∿230 °C; colorless needles from ethanol; MS m/e (relative intensity) 334 (100) M^+, 315 (14) M^+ - F, 314 (11) M^+ - HF, 167 (18) M^+ - C_6F_5; ^1H NMR δ 8.57 (d, 1, J = 8HZ, 3-H), 8.07 (d, 1, J = 8Hz, 4-H), 7.33, 7.44, 7.57, 8.17 (m, 4, 5∿8-H); ^{19}F NMR δ 21.6 (t-d, 2, J = 22Hz and 7Hz, 2,6-F), 0.9 (t-d, 2, J = 22Hz and 7Hz, 3,5-F), 9.1 (t, 1, J = 22Hz, 4-F); Milli-MS Found M^+ 334.0546, Calcd. as $C_{17}H_7F_5N_2$ 334.0529.

Dehydrogenation of III with selenium dioxide

By a procedure similar to that described above for I, III (3.80g, 10 mmol) was dehydrogenated with selenium dioxide (2.22g, 20 mmol) and 2.39g (71.5% yield) of IV was obtained.

Condensation of indole with PFBA in propanol

To a solution of indole (2.34g, 20 mmol) in propanol (50ml), PFBA (1.96g, 10 mmol) was added, and the solution was heated at reflux for 24 hours under argon. After evaporation, the residual material was crystallized from ethanol to give 2.81g of (pentafluorophenyl)bis(3-indolyl)methane (VI) as colorless grains, mp. 129∿130 °C; MS m/e (relative intensity) 412 (100) M^+, 411 (21) $M^+ - H$, 245 (54) $M^+ - C_6F_5$; ^1H NMR δ 6.31 (s, 1, CH), 7.92 (broad s, 2, NH), 6.89 (broad s, 2, 2-H), 7.05, 7.18, 7.32, 7.40 (m, 8, 4∿7-H); ^{19}F NMR δ 20.5 (d-d, 2, J = 21Hz and 7Hz, 2,6-F), - 0.3 (t-d, 2, J = 21Hz and 7Hz, 3,5-F), 4.6 (t, 1, J = 21Hz, 4-F); Milli-MS Found M^+ 412.0917, Calcd. as $C_{23}H_{13}F_5N_2$ 412.0997. The mother liquor was evaporated to dryness and the residual material was separated on a silica gel column (100ml, hexane-dichloromethane, 1:1). There were obtained an additional 0.57g (82.0% total yield) of VI and unreacted indole (0.37g).

Condensation of indole with PFBA in acetic acid

To a solution of indole (2.34g, 20 mmol) in acetic acid (50ml), PFBA (1.96g, 10 mmol) was added and the solution was heated at reflux for 24 hours under argon. The reaction mixture was evaporated to dryness and the deep red residual material was decolorized on a silica gel column (100 ml, eluted with hexane-dichloromethane 1:1). Recrystallization from ethanol gave VI (3.22g, 78.1% yield).

All the products synthesized in this work are new compounds.

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