POLYFLUORINATED HETEROCYCLIC COMPOUNDS

VII.* SYNTHESIS OF 4,5,6,7-TETRAFLUOROTRYPTOPHAN; 4,5,6,7-TETRAFLUOROHETEROAUXIN; AND 4,5,6,7-TETRAFLUOROTRYPTAMINE

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The synthesis of 4,5,6,7-tetrafluorotryptophan; 4,5,6,7-tetrafluoroheteroauxin; and 4,5,6,7-tetrafluorotryptamine from 4,5,6,7-tetrafluoro-3-(N-piperidinomethyl)indole or its quaternary salt with dimethyl sulfate is described.

In this communication we describe the synthesis of polyfluorinated analogs of several important, physiologically active compounds of the indole series such as tryptophan, heteroauxin, and tryptamine. Condensation of 4,5,6,7-tetrafluoro-3-(N-piperidinomethyl)indole (I) [1] or its quaternary salt with dimethyl sulfate (II) with acetamidomalonic ester leads to the formation of diethyl acetamido(4,5,6,7-tetrafluoro-3-indolyl)malonate (III). The hydrolysis of the latter with 20% hydrochloric acid gives β-(4,5,6,7-tetrafluoro-3-indolyl)-α-alanine (4,5,6,7-tetrafluorotryptophan) (IV), which was isolated from the reaction mixture by means of ion-exchange chromatography. Tryptophan IV gives a characteristic reaction for an amino acid with ninhydrin and is smoothly acylated by acetic anhydride to form β-(4,5,6,7-tetrafluoro-3-indolyl)-N-acetyl-α-alanine. Its structure was also confirmed by its IR and UV spectra.

4,5,6,7-Tetrafluoro-3-indolylacetic acid (4,5,6,7-tetrafluoroheteroauxin) (VI) was obtained by heating quaternary salt II with sodium cyanide in dimethylformamide with subsequent hydrolysis of the resulting nitrile (V) and by the action on I of sodium cyanide in aqueous alcohol. The structure of heteroauxin VI was confirmed by conversion to the known 4,5,6,7-tetrafluoroskatole by thermal decarboxylation [1]. Reduction of nitrile V with lithium aluminum hydride in ether leads to 4,5,6,7-tetrafluoro-3-(β-aminoethyl)indole (4,5,6,7-tetrafluorotryptamine) (VII), the structure of which was confirmed by its IR and UV spectra.

EXPERIMENTAL

The IR spectra were obtained with a UR-10 spectrometer. A strong absorption band at 1500 cm^{-1} (fluorinated benzene ring) was observed in the IR spectra of all of the fluorinated compounds. The UV spectra were obtained with an SFD-2 spectrometer with molar concentrations of $2 \cdot 10^{-4}$ and a layer thickness of 0.5 cm.

Diethyl Acetamido(4,5,6,7-tetrafluoro-3-indolyl)malonate (III). A) Sodium hydride [0.034 g (1.41 mmole)] was added to a solution of 0.30 g (1.38 mmole) of acetamidomalonic ester in 40 ml of dimethyl formamide, the mixture was heated at 90 deg for 1 h, 0.57 g (1.38 mmole) of II was added, and the mixture was held at 90 deg for 3 h. The mixture was then poured into water, and the resulting precipitate was filtered and dried to give 0.42 g (73%) of III with mp 195-196 deg (from aqueous alcohol). Found %: C 52.05, 51.69; H 4.32, 4.11; F 17.99, 18.00; N 7.11, 7.38. $C_{18}H_{18}F_4N_2O_5$. Calc. %: C 51.67; H 4.31; F 18.18; N 6.70.

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* See [1] for communication VI.

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IR spectrum (in KBr), cm^{-1}: 1670 (amide C=O), 1740 (ester C=O), 2800-3000 (CH, CH_2, and CH_3), 3400 (amide NH), and 3490 (indole NH).

B) A mixture of 0.12 g (0.55 mmole) of acetamidomalonic ester, 26 ml of toluene, and 0.02 g (0.5 mmole) of NaOH was refluxed for 1 h; 0.14 g (0.49 mmole) of I was added; and the mixture was refluxed for 5 h. The precipitate that resulted on cooling was filtered to give 0.13 g (63%) of III with mp 194-195 deg, which was identical to the preparation obtained in the previous experiment.

4,5,6,7-Tetrafluorotryptophan (IV). A solution of 0.29 g (0.7 mmole) of III in 40 ml of 20% hydrochloric acid was refluxed for 10 h, after which it was passed through a column packed with Dowex-50W × 4 ion-exchange resin in the H^+ form. The column was washed with water to neutrality, with alcohol, and again with water. The amino acid was eluted with 2 N ammonium hydroxide until the color formed with ninhydrin vanished. The ammoniacal eluate was evaporated to dryness in vacuo at no higher than 30 deg to give 0.14 g (73%) of IV with mp 263-265 deg (dec., from 35% aqueous alcohol). Found %: C 48.19, 48.29; H 2.90, 2.92; F 27.60, 27.86; N 9.35, 9.39. $C_{11}H_8F_4N_2O_2$. Calc. %: C 47.83; H 2.90; F 27.54; N 10.14. IR spectrum (in KBr), cm^{-1}: 1670 (NH_3^+), 1600 (COO^-), 2850-3000 (CH, CH_2), and 3490 (NH). UV spectrum: λ_{max} (log ε), nm: 262 (3.38). Heating IV with acetic anhydride for 5 min gave β-(4,5,6,7-tetrafluoro-3-indolyl)-N-acetyl-α-alanine with mp 243-246 deg. Found %: F 20.40, 20.38; N 7.42, 7.50. $C_{15}H_{12}F_4N_2O_4$. Calc. %: F 21.11; N 7.78. IR spectrum (in KBr), cm^{-1}: 1650 (amide C=O), 2800-3000 (CH, CH_2), and 3400 (amide NH).

4,5,6,7-Tetrafluoro-3-cyanomethylindole (V). A mixture of 0.41 g (1.0 mmole) of II and 0.18 g (3.7 mmole) of sodium cyanide in 6 ml of dimethylformamide and 2 ml of water was refluxed for 2 h and poured into water, and the resulting precipitate was filtered to give 0.21 g (92%) of V with mp 129-130 deg [sublimation at 140 deg (20 mm)]. Found %: C 52.42, 52.35; H 1.75, 1.96; F 33.39, 33.57; N 12.00, 12.02; mol. wt. 228. $C_{10}H_4F_4N_2$. Calc. %: C 52.63; H 1.75; F 33.33; N 12.28; mol. wt. 228. IR spectrum (in CCl_4), cm^{-1}: 2240 (C≡N) and 3490 (NH).

4,5,6,7-Tetrafluoroheteroauxin (VI). A) A mixture of 0.2 g (0.88 mmole) of V and 5 ml of 20% KOH was refluxed for 4 h and filtered, and the filtrate was acidified with 20% hydrochloric acid to pH 1. The precipitate was washed with water and dried to give 0.15 g (69%) of VI with mp 206-208 deg. Found %: C 48.66, 48.40; H 2.10, 2.27; F 29.88, 29.85; N 5.96, 5.70. $C_{10}H_5F_4NO_2$. Calc. %: C 48.58; H 2.02; F 30.77; N 5.69. IR spectrum (in KBr, cm^{-1}: 1710 (acid C=O), 2500-3000 (OH), and 3490 (NH). UV spectrum (in 0.1 N NaOH), λ_{max} (log ε), nm: 222 (3.32) and 253 (2.95).

B) A mixture of 0.2 g (0.70 mmole) of I, 0.53 g (10.8 mmole) of sodium cyanide, 5 ml of ethanol, and 3.5 ml of water was refluxed for 10 h. The mixture was evaporated to dryness, and 20% aqueous KOH was added to the solid residue. The mixture was refluxed for 4 h and filtered, and 20% hydrochloric acid was added carefully to pH 1. The resulting precipitate was filtered to give 0.06 g (35%) of VI, which was identical to the preparation obtained by method A.

4,5,6,7-Tetrafluorotryptamine (VII). A solution of 0.36 g (1.58 mmole) of V in 4.5 ml of ether was added slowly with stirring to a suspension of 0.25 g of lithium aluminum hydride in 10 ml of ether. The mixture was stirred for 5 h at 30-40 deg, and 5 ml of water and 2 ml of 20% aqueous NaOH were added carefully. The mixture was filtered, and the ether layer was separated and dried with $MgSO_4$. The cooled solution was saturated with hydrogen chloride to give 0.26 g (62%) of the hydrochloride of VII with mp 305-306 deg (in a sealed capillary, from benzene–ethanol). Found %: C 45.20, 45.21; H 3.42, 3.47; Cl 12.55, 12.75; F 28.10, 28.13; N 10.32, 10.26. $C_{10}H_8F_4N_2 \cdot HCl$. Calc. %: C 44.69; H 3.35; Cl 13.22; F 28.30; N 10.43. An aqueous solution of the hydrochloride of VII was treated with 10 ml of 15% ammonium hydroxide, and the resulting precipitate was filtered to give 0.21 g (93%) of VII with mp 136-138 deg (from aqueous alcohol). Found %: C 51.34, 51.38; H 3.15, 3.00; F 32.20, 32.28; F 12.06, 12.27. $C_{10}H_8F_4N_2$. Calc. %: C 51.72; H 3.45; F 32.76; N 12.07. IR spectrum (in CCl_4), cm^{-1}: 2800-3000 (CH, CH_2), 3310-3390 (two bands, NH_2), and 3490 (NH). UV spectrum (in alcohol), λ_{max} (log ε), nm: 212 (4.58) and 262 (3.65).

LITERATURE CITED

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