SYNTHESIS OF FLUORINATED ANALOGS OF HEMATOPORPHYRIN. II[1]

Masaaki Omote, Akira Ando, Mayumi Koyama, Toshiyuki Takagi, and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

This paper is dedicated to Doctor Arnold Brossi on the occasion of his 70th birthday.

Abstract -- With the aim of obtaining a porphyrin derivative useful for diagnosis and therapy of cancer, fluorinated analogs of hematoporphyrin, which had a trifluorohydroxyethyl group in the place of one of the hydroxyethyl groups, were synthesized by acetylation of trifluorohydroxyethyldeuteroporphyrin dimethyl esters, followed by reduction of the acetyl group.

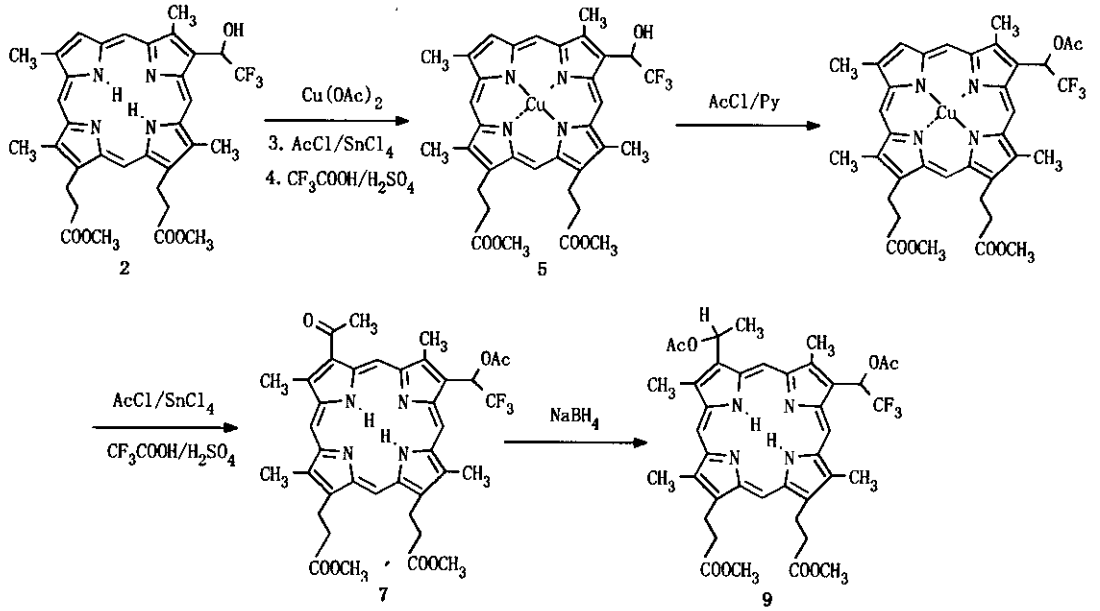
Some porphyrin derivatives are localized to tumor tissue, and recently photoradiation therapy using lasers has been suggested to have clinical value.[2] In the early stage of our work, hematoporphyrin derivative (HPD) attracted our attention. Although the structure of the active component of HPD has been proposed to be a dimer of hematoporphyrin,[3] it has generally been (and is still) used as a complex mixture of various porphyrins. We thought that if we could synthesize a porphyrin derivative that localized specifically to a certain tumor tissue or certain cancer cells, it would be potentially useful for diagnosis and therapy of cancer. For this purpose, we have synthesized fluorinated analogs of protoporphyrin[4] and hematoporphyrin,[5] some of which were taken up by some tumor cells preferentially. These results suggested that some porphyrins would localize to a certain cancer. As we mentioned in the previous report,[5] trifluorohydroxyethyldeuteroporphyrins showed interesting biological results. Now we tried to synthesize fluorinated analogs of hematoporphyrin, in which one of the two hydroxyethyl groups of hematoporphyrin was replaced with a trifluorohydroxyethyl group. In this report, we would like to report the results obtained during this synthetic research.

As mentioned in the previous work, deuteroporphyrin dimethyl ester (**1**) was treated with trifluoroacetaldehyde in the presence of a Lewis acid to give 3-, 8- and 3,8-bis-(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl esters (**2**, **3** and **4**). Now, we planned to introduce an acetyl group to **2** or **3** and to reduce the acetyl group to obtain the objective porphyrins.

Since deuteroporphyrins are sensitive to a strong acidic condition, **2** and **3** were converted to copper complexes (**5**) and (**6**) by treating with cupric acetate. First, we tried the acetylation of **5** in the presence of zinc chloride, followed by demetallation with trifluoroacetic acid and sulfuric acid. The yield of 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-acetyldeuteroporphyrin dimethyl ester (**7**) was only 24%. A similar reaction of **6** gave 8-(1-acetoxy-2,2,2-trifluoroethyl)-3-acetyldeuteroporphyrin (**8**) in the yield of only 37%. To improve the yields of this reaction, we acetylated the hydroxy group of **5** and used stannic chloride in place of zinc chloride, then we obtained **7** in the yield of 66%. A similar reaction of **6** did not proceed at all. Therefore, we used titanium tetrachloride as a catalyst and obtained **8** in the yield of 70%.

Finally, the acetyl group of **7** and **8** was reduced with sodium borohydride to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-(1-hydroxyethyl)deuteroporphyrin dimethyl ester (**9**) and 8-(1-acetoxy-2,2,2-trifluoroethyl)-3-(1-hydroxyethyl)deuteroporphyrin dimethyl ester (**10**) in the yields of 85% and 88%, respectively. Scheme 1 shows synthesis of **9**

Scheme 1



In conclusion, we could obtain two fluorine analogs of hematoporphyrin. In the course of this synthesis, a remarkable difference of reactivities between 3- and 8- positions of the porphyrin ring depending on the catalysts was observed. These compounds were hydrolysed in a conventional procedure and their accumulations to cancer are now being examined. The results will be reported elsewhere.

EXPERIMENTAL

3-(2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester Cu Complex (5). To a solution of 3-(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**2**, 847 mg, 1.33 mmol) in CH_2Cl_2 (56 ml) and MeOH (7.4 ml), $Cu(OAc)_2$-H_2O (399 mg, 2.00 mmol) was added, and the mixture was refluxed for 1 h, then concentrated under vacuum. The residue was purified on a column chromatography (SiO_2, CH_2Cl_2-AcOEt, 85:15) to give **5** (902 mg, 97%, red crystals, mp 232-234 ℃).

8-(2,2,2-Trifluoro-1-hydroxyethyl)deuteroporphyrin Dimethyl Ester Cu Complex (6). 8-(2,2,2-trifluoro-1-hydroxyethyl)deuteroporphyrin dimethyl ester (**3**, 638 mg, 1.00 mmol) was treated similarly as shown above to give the copper complex (**6**, 632 mg, 90%, red crystals, mp 250-252 ℃).

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-acetyldeuteroporphyrin Dimethyl Ester (7). To a solution of **5** (1.857 g, 2.66 mmol) in CH_2Cl_2 (100 ml), AcCl (350 μl, 3.19 mmol) and dry pyridine (300 μl, 3.71 mmol) were added, and the mixture was stirred at room temperature for 24 h, then poured on ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was purified on a column chromatography (SiO_2, CH_2Cl_2-AcOEt, 95:5-70:30) to give an acetate (1.825 g, 93%, red crystals). To a solution of the acetate (50 mg, 0.07 mmol) in CH_2Cl_2 (3 ml), AcCl (60 μl, 0.84 mmol) was added, then at -50 ℃ $SnCl_4$ (12 μl, 0.10 mmol) was added to this mixture. The mixture was stirred at this temperature for 1 h, then poured on ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The residue was treated with CF_3COOH (0.8 ml) and conc. H_2SO_4 (0.08 ml) at 0℃ for 1 h. The mixture was poured on ice-water, and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified on a column chromatography (SiO_2, CH_2Cl_2-AcOEt, 95:5-70:30) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-acetyldeuteroporphyrin dimethyl ester (**7**, 32 mg, 66%), mp 198-200 ℃. Ms *m/z*: 720 (M^+). HRms Calcd for $C_{38}H_{39}N_4O_7F_3$ (M^+): 720.2771. Found: 720.2769. ^{1}H-Nmr ($CDCl_3$) δ: 10.49 (1H, s), 10.46 (1H, s), 9.88 (1H, s), 9.45 (1H, s), 7.90 (1H, q, J=7.0 Hz), 4.05 (2H, t, J=7.5 Hz), 4.03 (2H, t, J=7.5 Hz), 3.595 (3H, s), 3.590 (3H, s), 3.40 (3H, s), 3.38 (3H, s), 3.25 (3H, s), 3.08 (2H, t, J=7.5 Hz), 3.07 (2H, t, J=7.5 Hz), 2.48 (3H, s), -3.95 (2H, s). ^{19}F-Nmr ($CDCl_3$, ppm from BTF): -11.37 (3F, d, J=6.9 Hz).

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-acetyldeuteroporphyrin Dimethyl Ester (8). The copper complex (**6**) (652 mg, 0.93 mmol) was treated with AcCl (120 μl, 1.69 mmol) and dry pyridine (100 μl, 1.24 mmol) as in the case of **5** to give the corresponding acetate (683 mg, 99%, red crystals). To a solution of this acetate (50 mg, 0.07 mmol) in CH_2Cl_2 (3 ml), AcCl (60 μl, 0.84 mmol) was added under ice-cooling and $TiCl_4$ (11.1 μl, 0.10 mmol) was added at this temperature. The mixture was stirred at 25 ℃ for 1.5 h, poured on ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was worked up as in the case of **7** to give **8** (34 mg, 70%), mp 150-153 ℃. Ms *m/z*: 720 (M^+). HRms Calcd $C_{38}H_{39}N_4O_7F_3$ (M^+): 720.2771. Found: 720.2774. ^{1}H-Nmr ($CDCl_3$) δ: 10.85 (1H, s), 10.30 (1H, s), 9.85 (1H, s), 9.74 (1H, s), 7.86 (1H, q, J=7.0 Hz), 4.32 (2H, t, J=7.8 Hz), 4.25 (2H, t, J=7.8 Hz), 3.85 (3H, s), 3.67 (3H, s), 3.64 (3H, s), 3.62 (3H, s), 3.61 (3H, s),

3.42 (3H, s), 3.25 (2H, t, J=7.8 Hz), 3.22 (3H, s), 3.19 (2H, t, J=7.8 Hz), 2.45 (3H, s), -3.71 (2H, s). ^{19}F-Nmr ($CDCl_3$, ppm from BTF): -11.39 (3F, d, J=6.7 Hz).

3-(1-Acetoxy-2,2,2-trifluoroethyl)-8-(1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (9). To an ice-cooled solution of **7** (61 mg, 0.08 mmol) in dry CH_2Cl_2 (19 ml) and MeOH (2.8 ml), $NaBH_4$ (97 mg, 2.56 mmol) was added portion-wise, and the mixture was stirred for 45 min, then poured on ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified on a column chromatography (SiO_2, CH_2Cl_2-AcOEt, 95:5-70:30) to give 3-(1-acetoxy-2,2,2-trifluoroethyl)-8-(1-hydroxyethyl)deuteroporphyrin dimethyl ester (**9**, 52 mg, 85%), mp 201-203 ℃. Ms *m/z*: 722 (M^+). HRms Calcd $C_{38}H_{41}N_4O_7F_3$ (M^+): 722.2927. Found: 722.2928. ^{1}H-Nmr ($CDCl_3$) δ: 10.41 (1H, s), 10.36 (0.5H, s), 10.35 (0.5H, s), 10.12 (1H, s), 9.97 (1H, s), 7.84 (0.5H, q, J=7.5 Hz), 7.83 (0.5H, q, J=7.5 Hz), 4.34 (2H, t, J=7.8 Hz), 4.32 (2H, t, J=7.8 Hz), 3.80 (3H, s), 3.70 (1.5H, s), 3.68 (1.5H, s), 3.66 (3H, s), 3.64 (3H, s), 3.61 (3H, s), 3.54 (1.5H, s), 3.52 (1.5H, s), 3.250 (2H, t, J=7.8 Hz), 3.247 (2H, t, J=7.8 Hz), 2.54 (0.5H, m), 2.49 (0.5H, m), 2.45 (1.5H, s), 2.44 (1.5H, s), 2.21 (1.5H, d, J=6.8 Hz), 2.19 (1.5H, d, J=6.8 Hz), -3.81(2H, s). ^{19}F-Nmr ($CDCl_3$, ppm from BTF): -10.31 (d, J=7.32 Hz).

8-(1-Acetoxy-2,2,2-trifluoroethyl)-3-(1-hydroxyethyl)deuteroporphyrin Dimethyl Ester (10). Compound (**8**) (76 mg, 0.11 mmol) was reduced with $NaBH_4$ (121 mg, 3.20 mmol) similarly as above to give **10** (67 mg, 88%), mp 203-205 ℃. Ms *m/z*: 722 (M^+). HRms Calcd $C_{38}H_{41}N_4O_7F_3$ (M^+): 722.2927. Found: 722.2912. ^{1}H-Nmr ($CDCl_3$) δ: 10.40 (1H, s), 9.98 (0.5H, s), 9.89 (0.5H, s), 9.68 (0.5H, s), 9.64 (0.5H, s), 9.54 (0.5H, s), 9.52 (0.5H, s), 7.89 (0.5H, q, J=7.3 Hz), 7.88 (0.5H, q, J=7.3 Hz), 5.30 (0.5H, m), 5.20 (0.5H, m), 4.25 (1H, t, J=7.8 Hz), 4.23 (1H, t, J=7.8 Hz), 3.40 (1H, t, J=7.5 Hz), 3.98 (1H, t, J=7.5 Hz), 3.71 (1.5H, s), 3.69 (1.5H, s), 3.68 (1.5H, s), 3.662 (1.5H, s), 3.656 (1.5H, s), 3.651 (1.5H, s), 3.624 (1.5H, s), 3.619 (1.5H, s), 3.31 (1.5H, s), 3.29 (1.5H, s), 3.21 (1H, t, J=7.8 Hz), 3.20 (1H, t, J=7.8 Hz), 3.10 (1H, t, J=7.5 Hz), 3.08 (1H, t, J=7.5 Hz), 2.87 (1.5H, s), 2.86 (1.5H, s), 2.50 (1.5H, s), 2.47 (1.5H, s), 1.66 (1.5H, d, J=6.1 Hz), 1.61 (1.5H, d, J=6.1 Hz), 1.25 (1H, s), -4.23 (2H, s). ^{19}F-Nmr ($CDCl_3$, ppm from BTF): -10.62 (1.5F, d, J=7.32 Hz), -9.98 (1.5F, d, J=7.32 Hz).

REFERENCES and NOTES

1. Part of this work was presented at the 114th Annual Meeting of Pharmaceutical Society of Japan, 1994, Tokyo.
2. Concerning the chemistry and biochemistry of HPD, see "Advances in Experimental Medicine and Biology", p.160, "Porphyrin Photosensitization", edited by D. Kessel and T. J. Dougherty, Plenum Press, New York, 1983.
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