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FLUOROPYRROLES AND TETRAFLUOROPORPHYRINS

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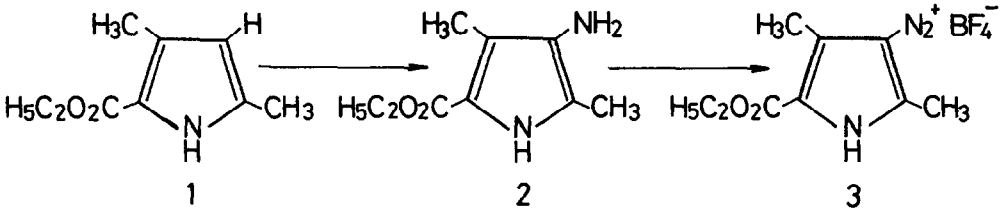
Abstract: Photolysis of pyrrole-β-diazonium tetrafluoroborates gave β-fluoropyrroles. These were further converted to 1,3,5,7-tetrafluoroporphyrins, the first example of ring-fluorinated porphyrin derivatives.

Much attention has recently been paid to fluorinated organic compounds from the viewpoints of their unique physico-chemical properties and biological activities. We are particularly interested in the pyrrole system, the unit of tetrapyrrole bio-pigments. Furthermore, some of naturally occurring halopyrroles isolated from marine sources show strong anti-bacterial activities. Although pyrroles having trifluoromethyl groups at α-[1] or β-position[2,3] are now available, there is no general route to the ring-fluorinated pyrroles.[4] We wish to report here a photochemical modification of the Schiemann reaction as a general method for the preparation of β-fluoropyrroles and also the first synthesis of ring-fluorinated porphyrin derivatives.

In the Scheme is shown the main synthetic route to β-fluoropyrrole (4) and 1,3,5,7-tetrafluoro-2,4,6,8-tetramethylporphyrin (6) with key intermediates. Other intermediates are shown in the general formulae. Ethyl 2,4-dimethyl-3-amino-5-carboxylate (2)[5] was prepared (55%) by reduction ($SnCl_2$ in acetic acid) of the azo dye (7)[6] derived from the β-free pyrrole (1) and p-nitrobenzenediazonium chloride. Aminopyrrole 2 was also obtained (91%) by reduction (Sn and HCl) of the nitropyrrole (8),[7] which in turn was prepared either by direct nitration (17%) of 1 or condensation (30%) of nitroacetone and ethyl 2-aminoacetoacetate hydrochloride. Treatment of 2 with $NaNO_2$ in fluoroboric acid afforded the diazonium tetrafluoroborate (3). Irradiation of the solution with a high pressure mercury lamp gave β-fluoropyrrole (4) in 17% yield.[8,9] The ^{19}F NMR spectrum showed a single absorption at 86 ppm upfield of CF_3CO_2H (external standard).

Oxidation of 4 with $Pb(OCOCH_3)_4$ (2.05 equiv) in acetic acid at 90°C gave 2-formyl (9)[10] and 2-acetoxy (10) derivatives[11] in 38 and 33% yields, re-



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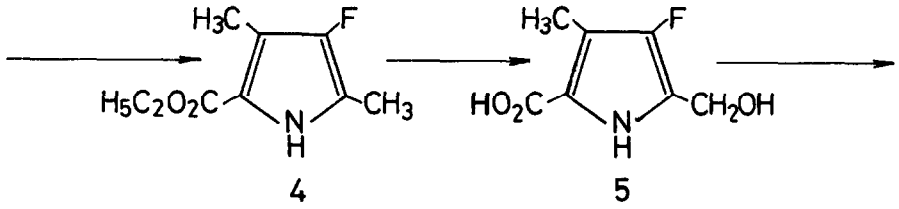

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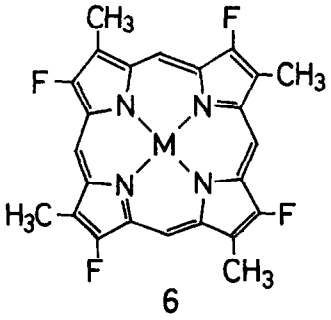

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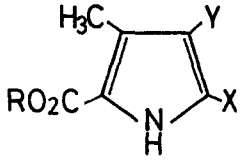

	X	Y	R
7 :	CH_3	N_2-C_6H_4-p-NO_2	C_2H_5
8 :	CH_3	NO_2	C_2H_5
9 :	CHO	F	C_2H_5
10 :	CH_2OCOCH_3	F	C_2H_5
11 :	CHO	F	H
12 :	CH_2OH	F	C_2H_5

spectively. Both pyrroles were further converted to carboxy-hydroxymethyl derivative (5)[12] in good yields upon reduction of the formyl and/or alkaline hydrolysis.[13] A mixture of 5 (0.61 g) and $K_3Fe(CN)_6$ (0.07 g) in acetic acid (7 mL) was refluxed for 1.5 h. The precipitates were filtered, washed with water and then methanol, dried and extracted into dichloromethane using a Soxlet extractor. Usual work-up and chromatography on silica gel with dichloromethane as eluant gave 1,3,5,7-tetrafluoro-2,4,6,8-tetramethylporphyrin (6, M = 2H) in 2% yield: mass spectrum m/e 438 (M^+) and 419 (M^+-19); H^1 NMR (CF_3CO_2D) δ ppm 10.89 (4H, s, meso-H) and 3.59 (12H, s, CH_3); ^{19}F NMR (CF_3CO_2D) 57.4 ppm upfield of CF_3CO_2D; electronic spectrum (CH_2Cl_2) λ_{max} (log ε) 387 (5.08), 489 (4.03), 518 (3.74), 559 (3.65), and 614 nm (3.28). In the copper-template synthesis, a mixture of 5 (0.45 g) and $Cu(OCOCH_3)_2$ (0.20 g) in acetic acid (15 mL) was refluxed for 1 h. Work-up and preparative thin layer chromatography afforded the Cu(II) complex (6; M = Cu(II)) in 3% yield: mass spectrum m/e 499 (M^+) and 480 (M^+-19); electronic spectrum (CH_2Cl_2) λ_{max} (log ε) 389 (5.03), 518 (3.84), and 552 nm (3.86). Treatment of the Cu(II) complex

with conc. H_2SO_4 at room temperature yielded the free-base porphyrin in quantitative yield. The electronic spectrum of 6 (M = 2H) is of the etio-type, in contrast to the phyllo-type absorption of 1,3,5,7-tetrakis(trifluoromethyl)-2,4,6,8-tetraethylporphyrin.[14]

Cyclic voltammetry of 6 (M = 2H) in dichloromethane with tetra-n-butylammonium perchlorate as a supporting electrolyte indicated that the first and second reduction took place at -1.17 and ∿-1.6 V vs. SCE as shown in Table I. The first ring reduction of 6 (M = Cu(II)) took place at -1.27 V. In Table I are also included reduction potentials of related porphyrin free-bases; $OEPH_2$ (eight ethyl groups), $TTfMH_2$ (four trifluoromethyl and four ethyl groups), and porphin (eight hydrogens). The trend in the change in redox potentials are readily understandable on the basis of the electronic effects of the substituents involved. interestingly, the present tetrafluoro free base (6) shows quite similar potentials to those of porphin, suggesting a counterbalance, as far as electrochemistry is concerned, of electron donation by methyl groups and electron withdrawal by fluoro substituents.

Table I. Redox Potential for Reduction of Porphyrin Free Bases

compound	substituent	$E_{1/2}$ (V vs. SCE) first	second
6 (M = 2H)	4 F, 4 CH_3	-1.17	∿-1.6
$OEPH_2$	8 C_2H_5	-1.46	-1.86
porphin	8 H	-1.18	-1.59
$TTfMH_2$	4 CF_3, 4 C_2H_5	-0.85	-1.18

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REFERENCES AND NOTES

1. Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami, and I. Nakano, Chem. Pharm. Bull. (Tokyo), 26, 1247 (1978).

2. H. Ogoshi, M. Homma, K. Yokota, H. Toi, and Y. Aoyama, Tetrahedron Lett., 24, 929 (1983).

3. J. Leroy, D. Cantacuzene, and C. Wakselman, Synthesis, 313, (1982); R. W. Kaesler, E. Legoff, J. Org. Chem., 47, 4779 (1982).

4. For a recent report on the preparation of N-alkyl-β-fluoropyrrole, see: J. Leroy, M. Rubinstein, and C. Wakselman, J. Fluorine Chem., 25, 255 (1984).

5. Mp 121-122°C (from ethanol-n-hexane); IR (KBr) 3370 and 3300 (NH_2) and 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 8.63 (1H, br s, NH), 4.32 (2H, q CH_2CH_3), 2.52

(2H, br s, NH_2), 2.24 and 2.20 (6H, both s, CH_3), and 1.37 (3H, t, CH_2CH_3).

6. IR (KBr) 1680 (CO), 1520 (NO_2), and 1450 cm^{-1} (N=N); ^1H NMR (CF_3CO_2D) δ 8.55 and 8.01 (4H, AB q, aromatic-H), 4.64 (2H, q, CH_2CH_3), 2.94 (6H, s, CH_3), and 1.54 (3H, t, CH_3).

7. P. C. Clezy, A. J. Liepa, and N. W. Webb, Aust. J. Chem., 25, 2687 (1972).

8. Mp 138°C (from ethanol-n-hexane); mass spectrum m/e 185 (M^+); IR (KBr) 3270 (NH) and 1660 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 8.63 (1H, br s, NH), 4.30 (2H, q CH_2CH_3), 2.23 (6H, s, CH_3), and 1.35 (3H, t, CH_2CH_3).

9. This photochemical method was applied to the preparation of fluoroimidazoles: K. L. Kirk and L. A. Cohen, J. Am. Chem. Soc., 95, 4619 (1973); K. L. Kirk, W. Nagai, and L. A. Cohen, ibid., 95, 8389 (1973).

10. Mp 133-133.5°C (from ethanol-n-hexane); mass spectrum m/e 199 (M^+); IR (KBr) 3270 (NH) and 1700 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 9.76 (1H, s, CHO), 9.30 (1H, br s, NH), 4.40 (2H, q, CH_2CH_3), 2.29 (3H, s, CH_3), and 1.41 (3H, t, CH_2CH_3).

11. Mp 110-110.5°C (from ethanol-n-hexane); mass spectrum m/e 243 (M^+); IR (KBr) 3300 (NH) and 1720, 1700, and 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 9.19 (1H, br s, NH), 5.00 (2H, s, CH), 4.32 (2H, q, CH_2CH_3), 2.23 (3H, s, CH_3), 2.07 (3H, s, $COCH_3$), and 1.36 (3H, t, CH_2CH_3).

12. Mass spectrum m/e 173 (M^+) and 154 (M^+-19); IR (KBr) 1640 (NH) and 1670 cm^{-1} (CO).

13. Alkaline hydrolysis of 9 yielded 11 (70%), which was reduced with $NaBH_4$ to 5 (64%). 11: mass spectrum m/e 173 (M^+) and 154 (M^+-19); IR (KBr) 1680 and 1650 cm^{-1} (CO); ^1H NMR ($CDCl_3$-C_5D_5N) δ 11.87 (1H, br s, CO_2H), 9.73 (1H, s, CHO), 9.67 (1H, br s, NH), and 2.33 (3H, s, CH_3). Alternatively, 9 was first reduced with $NaBH_4$ to 12 (94%), which was subsequently converted to 5 (88%) upon alkaline hydrolysis. 12: Mp 119-119.5°C (from ethanol); mass spectrum m/e 201 (M^+); IR (KBr) 3400 and 3300 (NH and OH) and 1685 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 9.23 (1H, br s, NH), 4.67 (2H, d, CH2OH), 4.32 (2H, q, CH_2CH_3), 2.23 (3H, s, CH_3), and 1.37 (3H, s, CH_2CH_3).

14. M. Homma, K. Aoyagi, Y. Aoyama, and H. Ogoshi, Tetrahedron Lett., 24, 4343 (1983).

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