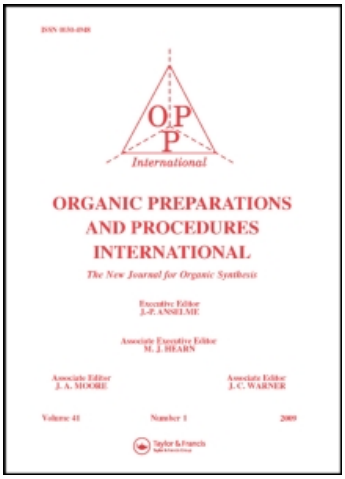

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SYNTHESIS OF DIFLUORODURENE AND DIFLUOROPYROMELLITIC ACID

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1/KChO/91-W, from the Polish Ministry of National Education. This support deserves our grateful thanks.

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1. Abbreviations used: Boc = *t*-butoxycarbonyl, z = benzyloxycarbonyl, Lys = lysine, Orn = ornithine, EDTA = ethylenediamine tetraacetic acid.

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SYNTHESIS OF DIFLUORODURENE AND DIFLUOROPYROMELLITIC ACID

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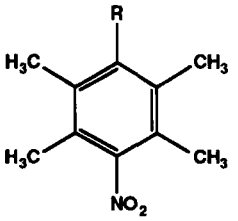
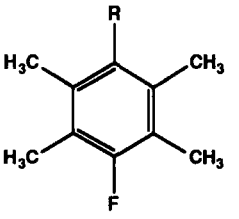
Practical molar scale syntheses of the commercially unavailable dichloro- and dibromopyromellitic acid by a two-step oxidation of the corresponding dihalodurenes have been developed earlier in this laboratory.[1] Our interest in the preparation of hitherto unknown difluoropyromellitic acid (**8**), required significant quantities of difluorodurene (**7**). Stavber and Zupan[2] had reported the isolation of small amounts (30 mg, 9% yield) of compound **7** from a mixture of products obtained by fluorination of durene with xenon difluoride. We now describe a six-step synthesis of difluorodurene (**7**) from readily accessible dinitrodurene (**1**)[3] and the oxidation of **7** to difluoropyromellitic acid (**8**).

Dinitrodurene (**1**) was reduced with sodium disulfide to *p*-aminonitrodurene,[4,5] isolated as its

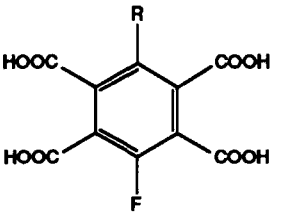
hydrochloride (**2**). The next three steps, *i. e.* the preparation of diazonium tetrafluoroborate (**3**) and its



1, R = NO_2
2, R = NH_2•HCl
3, R = $N_2^+ BF_4^-$
4, R = F



5, R = NH_2
6, R = $N_2^+ BF_4^-$
7, R = F



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decomposition to *p*-fluoronitrodurene (**4**) (Balz-Schiemann reaction) and also reduction of **4** to *p*-aminofluorodurene (**5**), were previously described by Grassini *et al.*[6] Decomposition of diazonium tetrafluoroborates is usually the critical step which limits the overall yield of the corresponding fluoroaromatic compounds. Conventionally, diazonium tetrafluoroborates are pyrolyzed as dry salts in what often results as an uncontrollable reaction. We have found that tetrafluoroborates (**3**) and (**6**) can be dediazonated under mild and fully controlled conditions by heating in refluxing *n*-hexane. In the case of **3**, a considerably better yield of **4** than that reported[6] was obtained. The diazotization procedure[6] was also simplified by conducting the reaction in 40% fluoroboric acid. Consecutive fluorodiazotization of **5** and dediazonation of **6** afforded the required difluorodurene (**7**) in 44% overall yield. Oxidation of **7** with 25% nitric acid at 150° in a sealed vessel followed by refluxing of the resultant mixture of difluorobenzenepolycarboxylic acids in an alkaline solution of potassium permanganate resulted in a good yield (57%) of difluoropyromellitic acid (**8**).

EXPERIMENTAL SECTION

All melting points were determined in capillary tubes with a Büchi melting point apparatus and are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Varian 200 MHz spectrometer in deuteriochloroform. Chemical shifts are in ppm from internal TMS for protons and carbon nuclei (positive downfield) and from internal $CFCl_3$ for fluorine nuclei (positive upfield). Dinitrodurene (**1**) was prepared according to a literature procedure.[3]

***p*-Aminonitrodurene Hydrochloride (2).**- Dinitrodurene (**1**) (20 g, 0.089 mole) was reduced with sodium disulfide by following a literature procedure.[5] The crude *p*-aminodurene was dissolved in 550 mL of 10% hydrochloric acid, filtered while hot, and left overnight in a refrigerator. A white crystalline solid containing small orange insertions was collected, recrystallized from 500 mL of 10% hydrochloric acid and dried over P_2O_5 to give **2** as white crystals (19.7 g, 96%), mp.~230° (dec.).

Anal. Calcd for $C_{10}H_5ClN_2O_2$: C, 52.06; H, 6.55; Cl, 15.37; N, 12.14
Found: C, 52.00; H, 6.62; Cl, 15.45; N, 12.08

***p*-Nitrodurenediazonium Tetrafluoroborate (3).**- To a vigorously stirred slurry of the hydrochlo-

ride (**2**) (19.5 g, 0.085 mole) in 40 g of 40% tetrafluoroboric acid and 80 mL of water, a solution of sodium nitrite (6.2 g, 0.09 mole) in 12 mL of water was added dropwise at 0-5° The yellow precipitate of **3** was collected, washed consecutively with small amounts (5 mL) of cold dilute tetrafluoroboric acid, ethanol and ether, dried for 3 hrs under vacuum and then overnight in the open atmosphere to yield a pale-yellow solid (23.7 g, 96%).

***p*-Fluoronitrodurene (4).**- Diazonium tetrafluoroborate (**3**) (23.5 g, 0.08 mole) was suspended in 400 ml of *n*-hexane and refluxed until evolution of nitrogen and boron trifluoride ceased (1 hr). The solution was decanted from a sticky tar to which 100 mL of *n*-hexane was added and refluxed for half an hour. Evaporation of the solvent from combined solutions on a water bath gave **4** as white-yellow crystals (12 g, 76%), mp. 98-99°, lit.[6] mp. 96-97°; ^{19}F NMR: δ 115.3 (s, 1F).

***p*-Aminofluorodurene (5).**- *p*-Fluoronitrodurene (**4**) (23 g, 0.117 mole) was reduced with tin metal by following a literature procedure[6] giving **5** as a crystalline solid (18 g, 92%), mp. 102-103°, lit.[6] mp. 100-101°. ^{19}F NMR (in deuterioacetone): δ 131.9 (s,1F).

***p*-Fluorodurenediazonium Tetrafluoroborate (6).**- *p*-Aminofluorobenzene (**5**) (13.5 g, 0.081 mole) was dissolved in 40 g of 40% tetrafluoroboric acid diluted with 50 mL of water (partial dissolution occurred) and diazotited with sodium nitrite (6 g, 0.087 mole), as described above for compound **3**, to give **6** as a white solid (17.7 g, 81.5%) which slowly decomposes on standing at room temperature.

Difluorodurene (7).- Diazonium tetrafluoroborate (**6**) (16.5 g, 0.062 mole) was refluxed in 300 mL of *n*-hexane and worked up as described above for compound **4**. Evaporation of the solvent gave pure **7** as white crystals (8.8 g, 84%), mp. 58.5-59.5°, lit.[2] mp. 55-56°. ^{1}H NMR: δ 2.12 (t, $^{4}J_{HF} = {}^{5}J_{HF}$ = 1.2 Hz, 12 H); ^{13}C NMR: δ 10.8 (t, $^{3}J_{CF} = {}^{4}J_{CF}$ = 4.1 Hz, 4C, CH_3), 121.3 (m, 4C, Arom.), 155.4 (d, $^{1}J_{CF}$ = 234 Hz, 2C, CF); ^{1}F NMR: δ 126.2 (br s, 2F).

Anal. Calcd for $C_{10}H_{12}F_2$: C, 70.56; H, 7.11; F, 22.33. Found: C, 70.60; H, 7.08; F, 22.38

Difluoropyromellitic Acid (8).- Difluorodurene (**7**) (6.4 g, 0.038 mole) and 150 mL of 25% nitric acid were placed in an open glass ampule. The ampule was closed in a stainless steel pressure tube, pressurized with 3 atm of nitrogen, and heated at 150° for 12 hrs. The detailed description of the equipment and procedure for the oxidation of dihalodurenes has been published previously.[1] The resulting solution was evaporated to give a mixture of dry difluorobenzenepolycarboxylic acids which were dissolved in 100 mL of 5% potassium hydroxide, brought to reflux, and potassium permanganate (13 g, 0.082 mole) was added portionwise during 4 hrs. The reaction mixture was refluxed overnight, then the excess of $KMnO_4$ was reduced by addition of small amount of methanol. The hot reaction mixture was filtered, the precipitate of MnO_2 was washed with boiling water and the combined filtrates, after cooling, were strongly acidified with conc. hydrochloric acid. The white suspension obtained was extracted with diethyl ether until all of the precipitate dissolved (9 x 200 mL) and the extract was dried over $MgSO_4$. The residue obtained after evaporation of the solvent was dried over P_2O_5 under vacuum to give pure acid **8** (no extraneous peaks in the NMR spectra) as a white solid (6.3 g, 57%), dec. > 230°; ^{1}H NMR (in DMSO-d_6): δ 14.3 (br, 4H); ^{13}C NMR: δ 124.8

(dd, $^2J_{CF}$ = 16.2 Hz, $^3J_{CF}$ = 7.3 Hz, 4C, Arom.), 151.4 (dd, $^1J_{CF}$ = 256 Hz, $^4J_{CF}$ = 4 Hz, 2C, CF), 163.0 (s, 4C, COOH); ^{19}F NMR: δ 119.3 (s, 2F). IR (nujol): 1730, 1700 (C=O), 1490, 1440 (Arom.) cm^{-1}. *Anal.* Calcd for $C_{10}H_4F_2O_8$: C, 41.40; H, 1.39; F, 13.10. Found: C, 41.45; H, 1.40; F, 13.20

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PREPARATION OF SOME PHOSPHOLIPID-TARGETED METRONIDAZOLE DERIVATIVES

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Nitroimidazoles such as metronidazole (**1**) are used clinically against a variety of anaerobic infections and are in trials in cancer therapy.[1] Efforts to improve the effectiveness of the drug have involved directing the nitroimidazole to an important biological target *via* structural modifications. In one approach, a DNA intercalating group, the phenanthridinium ion, was attached to the substrate's side-chain.[2] Interactions potentially also occur at the cell membrane, and to probe the effect of directing to this target, we decided to prepare phosphatidyl derivatives of nitroimidazoles by appropriate substitution in the side chain. Our approach involved the preparation of mixed phosphoric diesters, (RO)(R'O)PO_2H, which is a notoriously difficult task.[3] The present paper describes the synthetic methodology developed for the preparation of phosphoric diesters **2** derived from **1** and simple primary alcohols.

Since anilinium salts of monoalkyl phosphates **3** are readily available,[4] we used those