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Registry No. Glucose oxidase, 9001-37-0.

Pyridinium-1-ylcarbons: 1,2,3,3-Tetrakis(4-(dimethylamino)pyridinium-1-yl)-cyclopropene Tetrachloride and 1,1,2,3,3-Pentakis(4-(dimethylamino)pyridinium-1-yl)-allylide Tetrachloride

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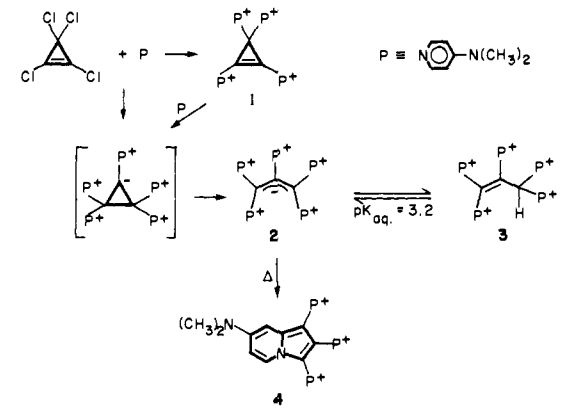
Poly-*N*-pyridinium compounds have been studied extensively for their biological activity.[1-15] Compounds having all available positions occupied by pyridinium groups have not been reported in the literature. Such compounds are polyionic, with a high concentration of charge, and may have unusual properties. We report here the synthesis in high yield of two such novel perpyridinium compounds from tetrachlorocyclopropene[16] and 4-(dimethylamino)pyridine (DMAP), 1,2,3,3-tetrakis(4-(dimethylamino)pyridinium-1-yl)cyclopropene tetrachloride (**1**), and 1,1,2,3,3-pentakis(4-(dimethylamino)pyridinium-1-yl)allylide tetrachloride (**2**).

Compound **1** was prepared in greater than 60% yield by direct reaction at 0 °C of tetrachlorocyclopropene with a solution of stoichiometric DMAP in 80% methylene chloride and 20% THF. The dry salt appears to be stable but is hygroscopic; the tetrakis(hexafluoroarsenate) is not hygroscopic. In water or methanol solution the compound reacts to give products not yet totally identified. In a chloroform solution, **1** reacts with DMAP to give **2**. This reaction supports the proposed intermediacy of **1** in the direct reaction to form **2** (see Scheme I). Identification of **1** is consistent with ^{1}H NMR,[17] ^{13}C NMR,[18] and IR (alkene stretch at 1635 cm^{-1}) spectroscopy and analysis of the tetrachloride and tetrakis(hexafluoroarsenate) salts.[19]

Scheme I



Compound **2** was prepared in greater than 60% yield by reaction of tetrachlorocyclopropene with DMAP in chloroform. The structure proposed is consistent with high-resolution ^{1}H NMR,[20] ^{13}C NMR,[21] and UV–vis (λ_{max} 450 nm) spectroscopy and analysis.[22] This remarkable compound, an allyl anion stabilized by five positive charges, forms dark red crystals that appear to be quite stable in air. Compound **2** can be protonated with HCl or HBF_4 to give the corresponding propene, **3**. The chloride salt of **3** shows four distinct pyridiniums in NMR spectroscopy. With the BF_4 salt of **3**,[23] exchange is rapid and only three types of pyridiniums are observed by ^{1}H NMR. Since **2** is intensely colored, and its protonated form **3** is not, the aqueous acidity of **3** could be determined by using the compound itself as the indicator. The pK_a of **3** is found to be 3.2 ± 0.1. This makes compound **3** the most acidic conjugate acid of an ylide for which data are reported.[24,25]

When **2** was heated to 190 °C under vacuum, 1 equiv of 4-(dimethylamino)pyridine hydrochloride sublimed, leaving 1,2,3-tris(4-(dimethylamino)pyridinium-1-yl)-7-(dimethylamino)-indolizine trichloride[26] (**4**) in greater than 60% yield, consistent with the known reactivity of pyridinium allylides[27,28] (Scheme I). The reaction of pyridine with tetrachlorocyclopropene to form indolizines was reported in an earlier paper.[29] The pyridine reaction apparently involves successive additions to the cyclopropene and elimination of chloride ion; with two and three pyridinium substituents, electrocyclic ring opening of the intermediate cyclopropyl anion competes successfully with further loss of chloride ion. With 4-(dimethylamino)pyridine, however, ring opening does not occur until all of the chlorines have been replaced.

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(17) δ, D_2O (J in hertz): 8.21 (4, d, J = 7.83), 8.02 (4, d, J = 7.81), 7.07 (4, d, J = 7.83), 6.91 (4, d, J = 7.83), 3.29 (12, s), 3.17 (12, s). $CDCl_3$: 9.88 (4, d, J = 7.8), 9.47 (4, d, J = 7.8), 7.11 (4, d, J = 7.8), 6.91 (4, d, J = 7.8), 3.35 (12, s), 3.24 (12, s).
(18) δ, D_2O (J in hertz): 163.4 (m), 145.32 (d, J_{CH} = 189.1), 144.28 (d, J_{CH} = 185.0), 115.87 (d, J_{CH} = 174.0), 115.35 (d, J_{CH} = 172.2), 108.14 (s), 74.77 (s), 47.34 (q, J_{CH} = 141), 46.69 (q, J_{CH} = 140).
(19) Analyses by Analytical Services Laboratory, UC College of Chemistry. Anal. Calcd for $C_{31}H_{40}N_8Cl_4 \cdot 6.5H_2O$ (chloride): C, 47.5; H, 6.8; N, 14.3; Cl, 18.1. Found: C, 47.3; H, 6.45; N, 14.5; Cl, 18.7. Calcd for $C_{31}H_{40}N_8As_4F_{24} \cdot (CH_3COCH_3)$ (hexafluoroarsenate): C, 30.5; H, 3.4; N, 8.4. Found: C, 30.4; H, 3.55; N, 8.5; Cl, 0. Acetone was found in the NMR spectrum.
(20) δ, D_2O (J in hertz): 7.90 (2, d, J = 7.5), 7.59 (4, d, J = 7.7), 7.58 (4, d, J = 7.6), 6.40 (10, m), 2.81 (12, s), 2.76 (18, s). CD_3OD: 8.81 (2, d, J = 7.66), 8.37 (8, dd, J = 7.94, 7.94), 4.93 (10, m), 3.27 (12, s), 3.23 (18, s).
(21) δ, D_2O: 49.6, 50.4, 50.6, 108.9, 117.3, 118.6, 119.1, 138.3, 150.9, 153.0, 153.1, 153.1, 153.5, 165.8, 167.4.
(22) Anal. Calcd for $C_{38}H_{50}N_{10}Cl_4 \cdot 6H_2O$: C, 50.9; H, 6.9; N, 15.6; Cl, 15.85. Found: C, 51.0; H, 7.1; N, 15.8; Cl, 16.05.
(23) Anal. Calcd for $C_{38}H_{51}N_{10}B_5F_{20} \cdot 2H_2O$ (BF_4 salt): C, 40.8; H, 4.9; N, 12.5. Found: C, 40.7; H, 5.0; N, 12.4; Cl, 0.
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(26) UV–vis (MeOH): λ_{max} 356 nm (log ϵ 4.16). ^{1}H NMR (CD_3OD) δ (J in hertz): 8.41 (d, 2, J = 8.0), 8.38 (2, d, J = 8.0), 8.32 (2, d, J = 7.8), 7.89 (1, d, J = 8.0), 6.95 (1, dd, J = 7.9, 2.5), 6.9 (6, m), 6.24 (1, d, J = 2.5), 3.36 (6, s), 3.30 (6, s), 3.25 (6, s), 3.04 (6, s). Anal. Calcd for $C_{31}H_{39}N_8Cl_3 \cdot 4.75H_2O$: C, 52.0; H, 6.8; N, 15.7; Cl, 14.9. Found: C, 52.0; H, 6.6; N, 15.5; Cl, 15.2.
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There appears to be a subtle and unexpected balance between the rates of cyclopropyl anion ring opening and loss of chloride ion that depends sensitively on the structure of the pyridine.

The first pyridinium-1-ylcarbons, **1** and **2**, show a chemistry that invites further study. They have the potential of opening up a whole new field of organic chemistry in which their high concentration of charge may provide exciting properties.

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Total Synthesis of C_{22}-Prostanoids in the E and F Series Based on Docosahexaenoic Acid

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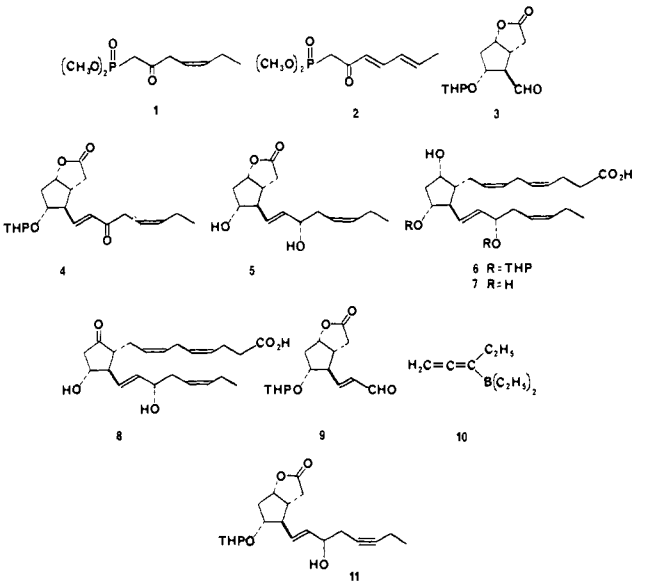
Docosa-4,7,10,13,16,19-(*Z*)-hexaenoic acid (docosahexaenoic acid, DCHA) is a major polyunsaturated fatty acid in marine lipid, along with eicosa-5,8,11,14,17-(*Z*)-pentaenoic acid (EPA). The obvious question as to whether DCHA might be the progenitor of a family of C_{22}-prostanoids, analogous to those derived from arachidonic acid or EPA, was made more intriguing by the reported isolation of a C_{22}-prostanoid of the F_α type from fish.[1] Although this claim has recently been retracted,[2] the key issue regarding the occurrence of C_{22}-prostanoids in marine organisms remains unresolved. It has been proposed that C_{22}-prostanoids can be synthesized in mammalian tissue from 7,10,13,16-(*Z*)-docosatetraenoic (adrenic) acid.[3] On the other hand, studies in these laboratories have shown that DCHA is not a substrate for mammalian PG synthetase from ram seminal vesicles or human platelets and is in fact a potent competitive inhibitor of the conversion of arachidonate to PGs (ca. 10^4 times that of aspirin on a molar basis).[4] In order to demonstrate whether C_{22}-prostanoids occur naturally and to evaluate their biological effects, it is clearly desirable to synthesize the compounds in question. We describe herein two processes for the synthesis of the E- and F_α-type prostaglandins which would be derived from DCHA. These syntheses employ standard PG precursors[5] and illustrate two new methods for generating the required ω-appendage which are applicable to the synthesis of PG_3s such as $PGF_{3\alpha}$ and PGE_3. Although the PG_3s have been synthesized previously,[6] their preparation until now has been much more difficult than those for the PG_1 or PG_2 series.

The first process for the synthesis of ω-3 PGs utilized as a key reagent dimethyl (*Z*)-(2-oxohept-4-enyl)phosphonate (**1**). This new substance was synthesized in two steps as follows. Reaction of methyl sorbate with the lithio derivative of dimethyl methylphosphonate[7] in tetrahydrofuran (THF) at −78 °C for 8 h afforded after extractive isolation and column chromatography on silica gel (sg) 52% of dimethyl (*E*,*E*)-(2-oxohepta-3,5-dienyl)-phosphonate (**2**) as a colorless liquid. Hydrogenation of freshly distilled **2** with 10 mol % of (methyl benzoate)chromium tricarbonyl[8] (750 psi H_2, methylene chloride, 140–150 °C, 1.5 h)



proceeded by stereospecific 1,4-addition to give, after sg chromatography and distillation, **1**, bp 90 °C (0.01 mm), in 77% yield. Horner–Emmons coupling of **1** with optically active aldehyde **3**,[6] unsuccessful under a wide variety of conditions, proceeded as desired by using a solution of sodium methoxide (methanol free) in dry THF at −78 °C for 1 min to convert **1** to its anion, promptly adding **3**, raising the temperature to 0 °C rapidly, and allowing the reaction to proceed at 0 °C for 3 h. Quenching with acetic acid, extractive isolation, and chromatography on sg provided keto lactone **4** in 50% yield.[9] Cleavage of the tetrahydropyranyl group of **4** (pyridinium tosylate in methanol at 50 °C for 1.5 h) and carbonyl reduction using diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide[10] at −78 °C in toluene afforded with 91:9 selectivity (85% yield) the required 15-*S*-diol **5** which readily separated from the less polar 15-*R* isomer by sg chromatography using 1:1 benzene–ethyl acetate for elution.[11] The minor 15-*R* isomer upon treatment with Attenburrow manganese dioxide in methylene chloride was converted to the corresponding 15-ketone and recycled.

Transformation of **5** into the bis(tetrahydropyranyl) ether of C_{22}-$PGF_{4\alpha}$ (**6**) was accomplished in 65% overall yield by the following sequence: (1) tetrahydropyranylation of **5** using 3 equiv of dihydropyran in methylene chloride with camphor-10-sulfonic acid catalyst at 0 °C for 20 min (99% yield); (2) lactone to lactol reduction using 1.6 equiv of diisobutylaluminum hydride in toluene at −78 °C for 30 min (99% yield); (3) Wittig reaction with the ylide from (*Z*)-7-(triphenylphosphonio)hept-4-enoate (generated using sodium bis(trimethylsilyl)amide in THF–toluene) at −40 °C then at 0 °C for 3.5 h; (4) esterification (CH_2N_2), sg chromatography and saponification.

The methyl ester of **6** was transformed into C_{22}-$PGF_{4\alpha}$ (**7**) by THP cleavage (pyridinium tosylate in methanol at 55 °C for 1 h) followed by saponificiation with 0.5 N sodium hydroxide in 50% aqueous methanol at 55 °C for 2.5 h (90% overall yield). Conversion of **6** to C_{22}-PGE_4 (**8**) was accomplished by Jones oxidation at 0 °C for 30 min followed by THP cleavage (6:3:1 acetic acid–water–THF, 35 °C for 8 h).

A second route to **5** was developed which also started from lactone aldehyde **3** via the enal **9**, which was produced from **3** by the sequence: (1) RCHO → $RCH{=}CHCOOC_2H_5$ chain extension using the sodium derivative of triethylphosphonoacetate

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