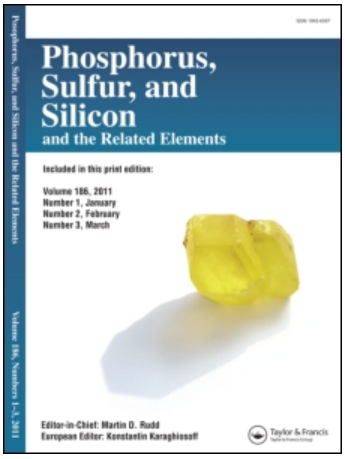

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CARBON-PHOSPHORUS HETEROCYCLES. STRUCTURAL ANALYSIS OF 1,2,3,4-TETRAHYDRO-1,4-DIMETHYL-1-PHENYL-PHOSPHINOLINIUM HEXAFLUOROPHOSPHATE AND 1,2,3,4-TETRAHYDRO-1-ETHYL-4-METHYL-1-PHENYLPHOS-PHINOLINIUM HEXAFLUOROPHOSPHATE. A NOVEL COCRYSTALLIZATION OF STEREOISOMERS OF THE FORMER

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CARBON-PHOSPHORUS HETEROCYCLES. STRUCTURAL ANALYSIS OF 1,2,3,4-TETRAHYDRO-1,4-DIMETHYL-1-PHENYL-PHOSPHINOLINIUM HEXAFLUOROPHOSPHATE AND 1,2,3,4-TETRAHYDRO-1-ETHYL-4-METHYL-1-PHENYLPHOSPHINOLINIUM HEXAFLUOROPHOSPHATE. A NOVEL CO-CRYSTALLIZATION OF STEREOISOMERS OF THE FORMER.

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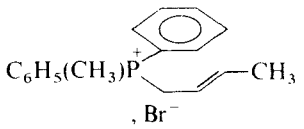
An analysis is provided for the cyclization of 2-butenyldiphenylmethylphosphonium bromide and 2-butenyldiphenylethylphosphonium bromide via the use of 115% polyphosphoric acid (PPA) at 160°C. In addition, the X-ray diffraction analysis of the crystalline products 1,2,3,4-tetrahydro-1,4-dimethyl-1-phenylphosphinolinium hexafluorophosphate and 1,2,3,4-tetrahydro-1-ethyl-4-methyl-1-phenylphosphinolinium hexafluorophosphate is discussed. An unusual co-crystallization occurs with the diastereoisomers of 1,2,3,4-tetrahydro-1,4-dimethyl-1-phenylphosphinolinium hexafluorophosphate which can be seen in the crystalline structure. Some screening data furnished by the National Cancer Institute is also evaluated in terms of carcinostatic activity versus the type of substitution on phosphorus.

INTRODUCTION

Recent discoveries that β-alkenyl-substituted phosphonium salts[1,2] (like **1** and **2**), β-alkenyl-substituted phosphine oxides,[3,4] and certain ω-carboxyalkylphosphonium salts[5] undergo cyclization in 115% polyphosphoric acid (PPA) have provided new entries to carbon-phosphorus (C-P) heterocycles.[6] Indeed, certain aralkenyl-substituted quaternary ammonium salts [5b] behaved similarly, attesting to the generality of the method for preparing selected, fused bicyclic C-P or certain N-containing heterocyclics. As part of the confirmation of the mechanism of cyclization for the β-alkenyl-substituted phosphonium salts, we herein report the structural analysis of two title compounds **3**[1] and **4**[1] via an X-ray diffraction examination of crystals. Moreover, an assessment of structure versus carcinostatic activity of several related structures is included.



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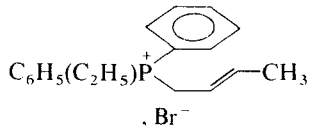

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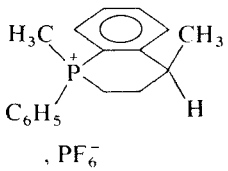
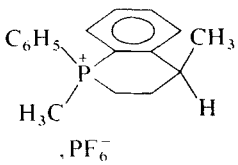
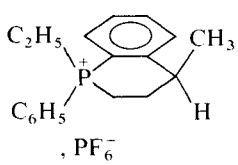


3a



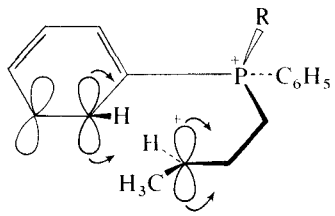
3b



4

RESULTS AND DISCUSSION

The conditions for the cyclization of **1** and **2** in hot PPA at 160°C have already been established.[1,2,7] If it is assumed that the reasonable intermediates **5** (from **1**, R = CH_3, or from **2**, R = C_2H_5) are formed, a concerted movement of *p* orbitals to form the new sigma bond in this thermal process could yield **3a** or **3b** (from **1**) or **4** (from **2**). Whether the ligands to the ring are apical-equatorial (**6a**) or equatorial-equatorial (**6b**) cannot be decided but both are apparently possible in six-membered phosphorinane systems.[8] In any case, **3a** (~25%) and **3b** (~75%) co-crystallized from the reaction mixture which was very dark and contained some polymeric material. From **2**, only **4** could be isolated since the amount of its diastereomer, if formed, must be small as it was not detected and since a dark polymer-appearing product was present in quantity.



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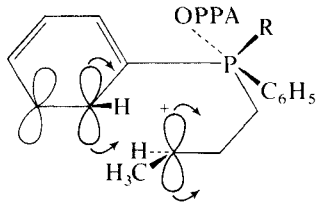
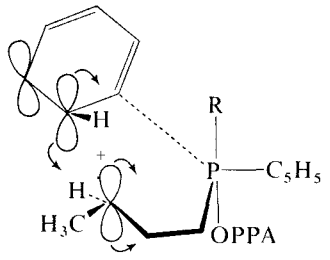


6a



6b

R = CH_3, C_2H_5

Indeed, when R = CH_3 (in **5**, **6**, **6a**), cyclization gives both diastereomers **3a** and **3b** but the ratios of the two found in the crystal need not be the same as that formed initially since some tarring occurs in the reactions. Thus, it is not possible to determine a true ratio of **3a**:**3b** formed in the reaction. Apparently, when R = C_2H_5, the diastereomer **4** is the only product which precipitates. A yield of 76% was reported[1] for **3** (**3a** and **3b**) and 42% for pure **4** but it was noted that **3** had a melting range of 179.5–182°C.[1] In the ^{1}HNMR spectrum of **3**, there appeared two doublets for the signal of protons of P-CH_3.[1,7] It is now clear that isomeric products (diastereomers via opposite configurations at P) co-crystallized but were individually solvated in $DCCl_3$. This is now substantiated by the X-ray diffraction data reported herein. All attempts to separate **3a** and **3b** failed since solubility properties were essentially identical in all solvents examined to date.

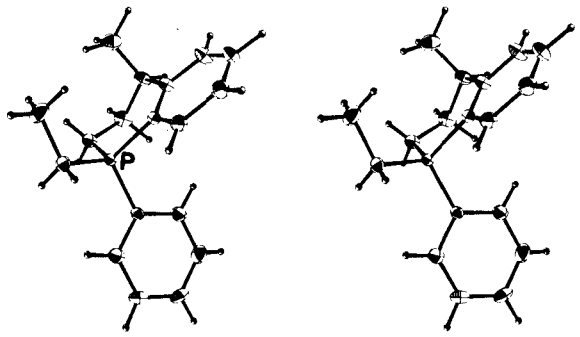


FIGURE 1 Stereoview of the cation of 1,2,3,4-tetrahydro-1,4-dimethyl-1-phenylphosphinolinium hexafluorophosphate (compound **3**).

Stereoviews of the cations of 1,2,3,4-tetrahydro-1-ethyl-4-methyl-1-phenyl-phosphinolinium hexafluorophosphate (**4**) and 1,2,3,4-tetrahydro-1,4-dimethyl-1-phenylphosphinolinium hexafluorophosphate (**3b**) are shown in Figures 1 and 2.

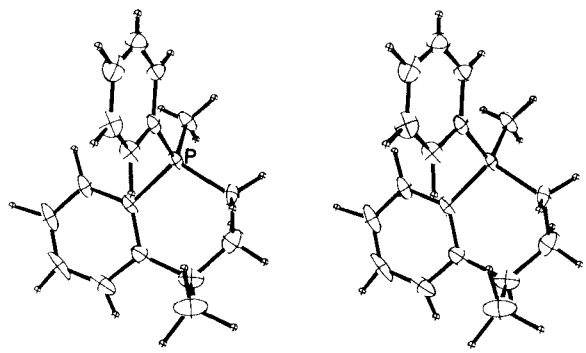


FIGURE 2 Stereoview of the cation of 1,2,3,4-tetrahydro-1-ethyl-4-methyl-1-phenylphosphinolinium hexafluorophosphate (compound **4**).

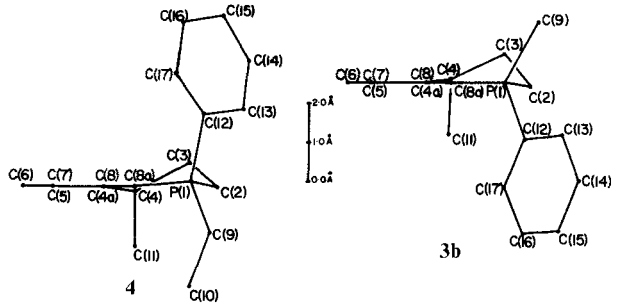


FIGURE 3 A comparative view of the molecules with respect to the least-squares plane through the aromatic part of the phosphinolinium ring.

Figure 3 shows a comparative view of the molecules with respect to the least-squares planes through the aromatic part of the phosphinolinium rings. From these figures, it can be seen that the conformation of the heterocyclic ring is very similar in both compounds. This conformation is also the same as the one found for 1,2,3,4-tetrahydro-1,4,4-trimethyl-1-phenylphosphinolinium hexafluorophosphate[9] (**7**), and this can be ascertained as well from the endocyclic torsion angles of the heterocyclic ring in compounds **3b**, **4**, and **7** (Table I). The relative configuration of the C(4) and P(1) substitutions, however, is different between compounds **3b** and **4**. In this respect, it is interesting to note that the last difference Fourier synthesis for compound **3b** showed two residual peaks (1.1–1.2 e/Å). These could be assigned to alternative positions for C(3) and C(11), which results in a flattening of the heterocyclic ring and a syn arrangement rather than anti-arrangement of the C(11) methyl group with respect to the C(9) methyl group. This alternative structure **3a** is present 25% of the time as judged from the peak heights in the difference Fourier synthesis. Interestingly, the stereoisomer **3a** occurring 25% of the time has the same relative configuration as compound **4**. It is rather unusual for two stereoisomers to co-crystallize, as observed in structure **3**. In compounds **4** and **7**, the H atoms attached to C(17) are situated above the heterocyclic ring, while in the predominant configuration of **3**, namely **3b**, the phenyl group extends somewhat further away from this ring.

The bond distances and angles (Figures 4, 5, and Table II) in both compounds are quite normal. The P^+-C (phenyl) distances are rather long [1.792(2) and 1.788(2) Å] due to steric hindrance. The P^+-methyl distance is shorter than the P^+-ethyl distance [1.783(2) and 1.797(2) Å], also presumably due to steric hindrance, and, in the heterocyclic ring, the P^+-C(sp^2) distances [1.788(2) and 1.776(3) Å] are shorter than the P^+-C(sp^3) bond lengths [1.795(3) and 1.795(3) Å]. Similar observations were made in **7**,[9] *cis*-5,10-dihydro-10-hydroxy-5,10-dimethyl-5-phenylacridophosphinium iodide,[10] and 1-ethyl-1,2,3,4-tetrahydro-1-phenylbenzo[*h*]phosphinolinium bromide,[11] although in

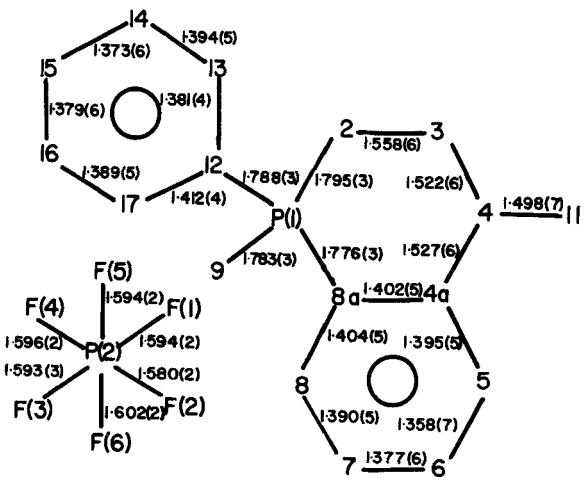


FIGURE 4 Bond distances in compound **3b**.

TABLE I

Torsion angles for **3b**, **4** and **7**

Compound				3b	4	7	Compound				3b	4
P(1)	C(2)	C(3)	C(4)	−64.2°	−60.4°	−66.5	C(5)	C(4a)	C(4)	C(11)	−76.5°	−81.5°
C(2)	C(3)	C(4)	C(4a)	61.1	59.9	56.7	C(8)	C(8a)	P(1)	C(12)	58.3	−64.7
C(3)	C(4)	C(4a)	C(8a)	−26.3	−31.2	−19.3	C(3)	C(2)	P(1)	C(9)	−85.8	153.5
C(4)	C(4a)	C(8a)	P(1)	−0.4	7.4	−2.1	C(8a)	P(1)	C(12)	C(17)	46.2	−38.7
C(4a)	C(8a)	P(1)	C(2)	−4.0	−7.9	−7.9	C(9)	P(1)	C(12)	C(13)	−13.4	21.3
C(8a)	P(1)	C(2)	C(3)	33.6	32.9	38.9	C(2)	P(1)	C(9)	C(10)		−63.0

Compound **7** is 1,2,3,4-tetrahydro-1,4,4-trimethyl-1-phenylphosphinolinium hexafluorophosphate.[9]

TABLE II

Bond angles

			3b	4				3b	4
C(8a)	P(1)	C(2)	106.6(1)	106.6(1)	C(4a)	C(8a)	C(8)	120.6(3)	121.4(2)
C(8a)	P(1)	C(9)	109.9(2)	110.7(1)	C(8a)	C(8)	C(7)	120.0(3)	120.0(2)
C(8a)	P(1)	C(12)	108.2(1)	107.3(1)	C(8)	C(7)	C(6)	119.1(3)	119.3(3)
C(2)	P(1)	C(9)	110.5(2)	111.0(1)	C(7)	C(6)	C(5)	120.8(4)	120.8(3)
C(2)	P(1)	C(12)	110.9(1)	111.2(1)	C(6)	C(5)	C(4a)	122.6(4)	121.3(3)
C(9)	P(1)	C(12)	110.6(1)	109.8(1)	C(5)	C(4a)	C(8a)	116.8(3)	117.2(2)
P(1)	C(2)	C(3)	109.0(2)	110.9(2)	P(1)	C(9)	C(10)		112.4(2)
C(2)	C(3)	C(4)	113.0(3)	113.6(2)	P(1)	C(12)	C(13)	123.1(2)	121.2(2)
C(3)	C(4)	C(4a)	113.0(4)	113.5(2)	P(1)	C(12)	C(17)	117.3(2)	119.4(2)
C(3)	C(4)	C(11)	115.8(4)	113.3(2)	C(12)	C(13)	C(14)	119.5(3)	120.0(2)
C(4a)	C(4)	C(11)	109.1(4)	109.3(2)	C(13)	C(14)	C(15)	120.8(4)	120.2(3)
C(4)	C(4a)	C(8a)	123.7(3)	124.0(2)	C(14)	C(15)	C(16)	120.4(4)	120.2(3)
C(4a)	C(8a)	P(1)	122.2(2)	121.5(2)	C(15)	C(16)	C(17)	119.9(3)	120.1(3)
C(4)	C(4a)	C(5)	119.4(4)	118.8(2)	C(16)	C(17)	C(12)	119.8(3)	120.2(2)
P(1)	C(8a)	C(8)	117.1(2)	117.0(2)	C(17)	C(12)	C(13)	119.6(3)	119.4(2)

TABLE III

Crystal and structure data for **3** and **4**

	3	**4**
Formula	$C_{17}H_{20}P.PF_6$	$C_{18}H_{22}P.PF_6$
F.W.	400.3	414.3
Space group	$P2_1/a$	$P2_1/a$
Molecules/unit cell(Z)	4	4
Unit cell dimensions at −160(2)°C	a = 12.093(2) Å b = 19.890(3) Å c = 7.585(2) Å β = 100.63(2)° V = 1793.1 Å^3	a = 15.134(4) Å b = 10.755(2) Å c = 13.037(2) Å β = 115.95(2)° V = 1908.0 Å^3
Unit cell dimensions at 20(2)°C	a = 12.240(1) Å b = 20.055(2) Å c = 7.782(2) Å β = 101.08(1)°	a = 15.52 Å b = 10.77 Å c = 13.19 Å β = 116.3°
D_c (at 20°C)	1.42 g.cm^{-3}	1.39 g.cm^{-3}
D_m (at 20°C) $(CCl_4/(C_2H_5)_2O)$	1.43 g.cm^{-3}	1.40 g.cm^{-3}
Radiation for unit cell dimensions	CuKα_1 (Ni-filtered) λ = 1.54051 Å	CuKα_1 (Ni-filtered) λ = 1.54051 Å
Radiation for intensity data	CuK$\bar{\alpha}$ (Ni-filtered) λ = 1.5418 Å	CuK$\bar{\alpha}$ (Ni-filtered) λ = 1.5418 Å
Scan mode	θ-2θ	θ-2θ
θ_{max}	75°	70°
Maximum scan time	60 s	60 s
Crystal dimensions	0.17 × 0.19 × 0.33 mm parallelopiped	0.06 × 0.31 × 0.41 mm parallelopiped
Total number of reflections	3699	3617
Number of unobserved reflections ($I < 2\sigma(I)$)	349	399
Absorption coefficient	27.44 cm^{-1}	25.98 cm^{-1}
$R = \frac{\Sigma\|kFo\| - \|Fc\|}{\Sigma\|kF_o\|}$ observed data only	0.061	0.040
R-value all data	0.071	0.052

the latter compound, the P^+-C(sp^2) bond length was found to be longer than the P^+-C(sp^3) distance. The size of the endocyclic bond angles at P^+ are quite similar in all of these five compounds, varying between 105.7° and 106.6°. It was also noted that in **3a** the C(9)–C(11) distance calculated to be 4.86 Å while in **4** the C(9)–C(11) distance was found to be 4.84 Å. Consequently there is probably little difference in ring distortions in both systems.

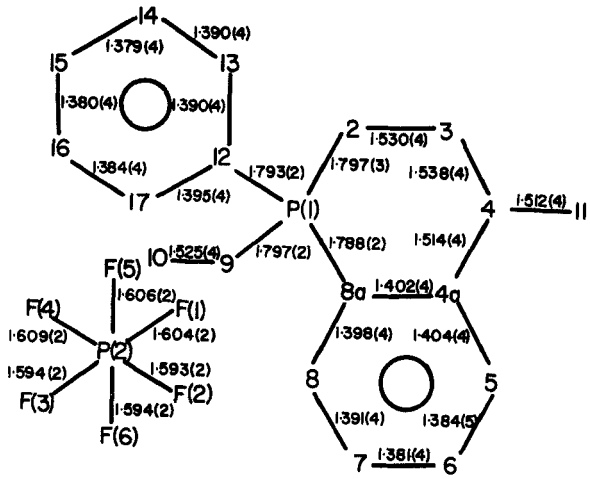


FIGURE 5 Bond distances in compound **4**.

With the structures of **3** and **4** now confirmed, it is possible to assess screening data on carcinostatic properties of each system as supplied by the NCI. Surprisingly, **1** (NSC–245853) and **2** (NSC–24393) displayed T/C values in the antitumor screens of the National Cancer Institute of 104 (Dose/Injection of 0.80 mg/kg) and 112 (Dose/Injection of 3.13 mg/kg), respectively, against P388 lymphocytic leukemia. Phosphinolinium salts **3a**/**3b** (NSC-248536) (ratio of isomers was 1/3) tested against L–1210 lymphoid leukemia screens gave a T/C value of 107 (Dose/Injection of 3.13 mg/kg) while **4** (NSC–245396) gave a maximum T/C of 121 (Dose/Injection of 6.25 mg/kg) in the same test system. In view of the finding that 1,2,3,4-tetrahydro-4-methyl-1,1-diphenylphosphinolinium chloride[7,12] (NSC–273810) had a T/C value of 155 (Dose/Injection of 25 mg/kg) in P388 lymphocytic leukemia screens, we tentatively conclude that the nature of the substituent on phosphorus is likely important for maximum activity as well as perhaps the constitution of the anion. This matter is being investigated further.

EXPERIMENTAL

Compounds **3**[1] and **4**[1] were recrystallized from dichloromethane by dropwise addition of ethyl ether. All diffraction data were

TABLE IV

Positional parameters ($\times 10^4$)

	Compound **3b**		
	x	*y*	*z*
P(1)	3077.0(6)	6088.3(4)	1231.4(10)
P(2)	2090.7(6)	9125.4(4)	3799.2(12)
F(1)	2119(2)	9160(1)	1709(3)
F(2)	2759(2)	8439(1)	3940(3)
F(3)	2048(2)	9079(1)	5882(3)
F(4)	1432(2)	9824(1)	3623(4)
F(5)	915(2)	8733(1)	3356(3)
F(6)	3255(2)	9522(1)	4229(3)
C(2)	3193(3)	6492(2)	3374(4)
C(3)	2222(4)	6242(2)	4301(6)
C(4)	1061(3)	6441(2)	3289(6)
C(4a)	794(3)	6149(2)	1398(5)
C(5)	−323(3)	6036(2)	595(7)
C(6)	−622(3)	5768(2)	−1072(6)
C(7)	184(3)	5586(2)	−2048(6)
C(8)	1313(3)	5690(2)	−1318(5)
C(8a)	1618(2)	5977(1)	394(4)
C(9)	3767(3)	5292(2)	1456(5)
C(11)	814(4)	7179(2)	3204(8)
C(12)	3640(2)	6609(1)	−309(4)
C(13)	4630(3)	6464(2)	−894(4)
C(14)	5013(3)	6898(2)	−2093(5)
C(15)	4422(3)	7468(2)	−2693(5)
C(16)	3431(3)	7620(2)	−2125(5)
C(17)	3029(3)	7194(2)	−937(5)
	Compound **4**		
P(1)	8239.0(4)	8175.9(5)	7843.2(4)
P(2)	4019.6(4)	6459.2(6)	1929.5(5)
F(1)	5035(1)	6827(1)	1899(1)
F(2)	4037(1)	7741(1)	2551(1)
F(3)	3013(1)	6075(2)	1959(1)
F(4)	4031(1)	5155(2)	1330(1)
F(5)	4624(1)	5825(1)	3157(1)
F(6)	3430(1)	7091(2)	711(1)
C(2)	7186(2)	7624(2)	8004(2)
C(3)	6553(2)	6777(3)	7010(2)
C(4)	6152(2)	7420(3)	5840(2)
C(4a)	6948(2)	7907(2)	5540(2)
C(5)	6756(2)	7977(3)	4386(2)
C(6)	7441(2)	8462(3)	4058(2)
C(7)	8334(2)	8901(3)	4859(2)
C(8)	8552(2)	8833(2)	6011(2)
C(8a)	7865(2)	8335(2)	6345(2)
C(9)	8658(2)	9640(2)	8557(2)
C(10)	7893(2)	10666(3)	8051(3)
C(11)	5432(2)	8453(3)	5708(3)
C(12)	9221(2)	7064(2)	8373(2)
C(13)	10020(2)	7218(2)	9432(2)
C(14)	10773(2)	6344(3)	9819(2)
C(15)	10718(2)	5310(3)	9169(2)
C(16)	9925(2)	5148(3)	8120(2)
C(17)	9180(2)	6024(2)	7716(2)

taken on a Nonius-CAD 4 automatic diffractometer. The crystal data and parameters for the intensity data are summarized in Table III. The data were corrected for Lorentz and polarization factors and for absorption.[13] Individual weights were calculated for all reflections.[14]

Both structures were solved by direct methods using the program MULTAN.[15] After the initial least-squares refinement, all H atoms in compound **4**, and all but four H atoms in compound **3** were located from difference Fourier syntheses. The least-squares refinement was completed using anisotropic thermal parameters for P, F and C atoms and isotropic temperature factors for H atoms. A final difference Fourier synthesis for compound **4** did not show any significant features, but the same calculation for compound **3** showed two significant peaks. (See previous discussion). The scattering factors were taken from the International Tables for X-Ray Crystallography[16] and from the work of Stewart, Davidson and Simpson.[17] The final positional parameters for the P, F and C atoms are given in Table IV. The anisotropic thermal parameters and the H atom parameters are available from the authors.

The T/C symbolism refers to the survival time of the test animals/survival time of the control animals as standardized by the National Cancer Institute.

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