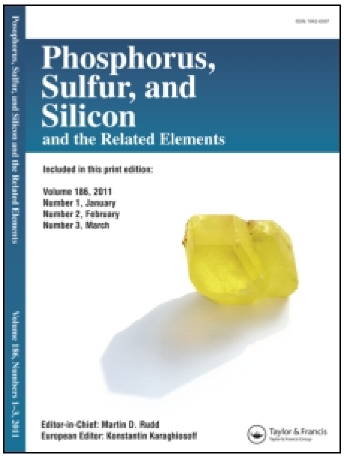

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ORGANOSULPHUR PHOSPHORUS ACID COMPOUNDS. PART 4. FLUOROBENZYLPHOSPHONO-SULPHONIC ACIDS

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To cite this Article Montoneri, E. , Savarino, P. , Viscardi, G. and Gallazzi, M. C.(1994) 'ORGANOSULPHUR PHOSPHORUS ACID COMPOUNDS. PART 4. FLUOROBENZYLPHOSPHONO-SULPHONIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 86: 1, 145 — 155

To link to this Article: DOI: 10.1080/10426509408018398

URL: http://dx.doi.org/10.1080/10426509408018398

Phosphorus, Sulfur, and Silicon, 1994, Vol. 86, pp. 145–155
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ORGANOSULPHUR PHOSPHORUS ACID COMPOUNDS. PART 4.†
FLUOROBENZYLPHOSPHONO-SULPHONIC ACIDS

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(Received August 31, 1993; in final form December 14, 1993)

Four new organosulphur phosphorus acid compounds have been obtained by sulphonation with liquid SO_3: 2-fluorobenzylphosphonic and 4-fluorobenzylphosphonic acids gave 2-fluorobenzylphosphono-5-sulphonic and 4-fluorobenzylphosphono-3-sulphonic acids respectively, in nearly quantitative yields; 3-fluorobenzylphosphonic acid gave 3-fluorobenzylphosphono-6-sulphonic acid (85%) and 3-fluorobenzylphosphono-4-sulphonic acid (15%). Product structures are based on ^{13}C magnetic resonance data. The entry of the SO_3H group into the aromatic ring seems mainly ruled by the fluorine substituent.

Key words: Sulphonation; fluorobenzylphosphonic acid; fluorobenzylphosphono-sulphonic acid.

Organosulphur phosphorus polyacids[1-3] are intermediates for the synthesis of layered metal salts, suitable for application in such areas as ion exchange, chemical separation, Brønsted acid catalysis and electrochemistry.[4-6] Zirconium arylphosphonates have been investigated as solid electrolytes and the presence of a sulphonic acid substituent in the aromatic ring has been proven to raise significantly the proton conductivity of these materials.[6] The availability of fluorobenzylphosphonosulphonic acids, $FC_6H_3(SO_3H)PO_3H_2$, for the above scopes seemed desirable since the additional fluorine substituent in the aromatic ring is expected to affect the properties of the acid functions.[7,8] To our knowledge, the above phosphono-sulphonic acids are not reported in the literature. This work is concerned with the sulphonation of fluorobenzylphosphonic acid by liquid SO_3 as a facile synthesis of the title compounds.

RESULTS AND DISCUSSION

Several fluorobenzylphosphono-sulphonic acids isomers were obtained (Figure 1), starting from diethyl fluorobenzylphosphonates[9] (see Experimental). Reactions (2, 4 and 6), shown in Figure 1, occurred readily at room temperature upon mixing

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†Previous work: Part I,[1] Part II,[2] Part III.[3]
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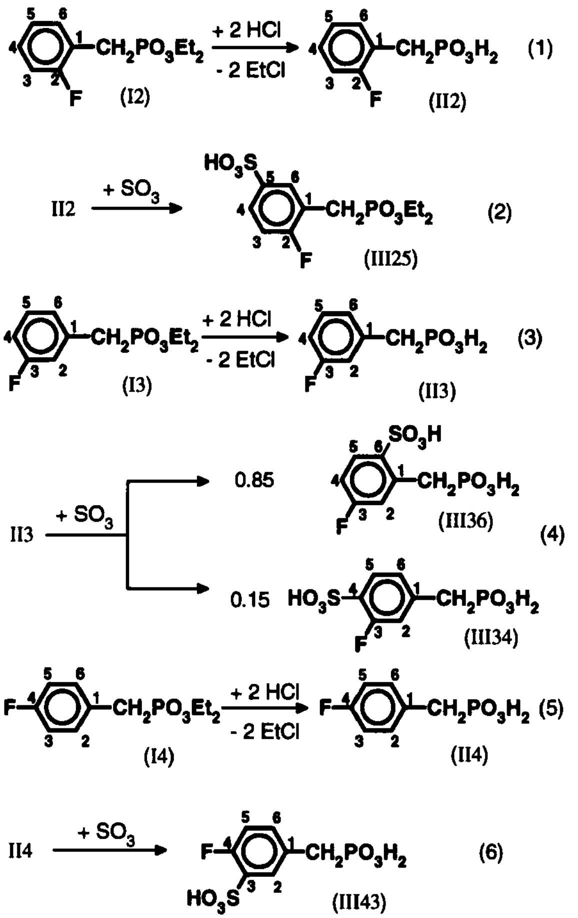

FIGURE 1 Structure and distribution of product isomers in the synthesis of fluorobenzylphosphonosulphonic acids. Reagents and product isomers throughout the paper are identified by the Roman numeral corresponding to the empirical formula, followed by one or two digits Arabic numerals identifying respectively the carbon bonded to fluorine and the carbon bonded to sulphur.

the reagents, and were well shifted to the right at SO_3/**II** molar ratio of 3.2; it was therefore possible to obtain **III** free from **II**. The direct sulphonation of the esters (**I2**, **I3**, or **I4**), followed by hydrolysis, gave also 2-hydroxyethane-sulphonic acid, which appeared difficult to separate from compounds **III**. Sulphonation of aliphatic carbon under these conditions has already been reported.[10]

Compounds **I** appear well characterized by ^{13}C n.m.r. spectroscopy in the literature.[9] Compounds **II** and **III**, so far unreported, are identified in this work as follows. Empirical formulas for compounds **II** and **III** are well in agreement with ^1H n.m.r. spectra (Table I) which contained resonance signals equivalent to the presence of four ring protons and of two methylene protons for compounds **II**, and to the presence of three ring protons and of two methylene protons for compounds **III**. Accordingly, the ^{13}C n.m.r. spectra (Table II) exhibited two quaternary carbon, four aromatic (H)C and one PCH_2 resonance signals for compounds **II**, and three

TABLE I

^{1}H magnetic resonance data for fluorobenzylphosphonic acids (**II**) and fluorobenzylphosphonosulphonic acids (**III**): chemical shift (δ, p.p.m.),[a] coupling constant (J, Hz)[b] and deshielding effect of SO_3H substituent ($\Delta\delta$, p.p.m.)[c]

	δ and J						
			ring protons				
Cpd[d]	PCH_2	protons	H2	H3	H4	H5	H6
II2	δ^c	3.27	δ^g	7.18	7.35	7.21	7.38
II2	J^f	21.2	J^h	9.52	7.81	7.81	7.80
II3	δ^c	3.22	δ^i 6.99		6.91	7.23	7.05
II3	J^f	22.5	J^h 9.81		8.64	8.64	7.72
II3			J^l			5.91	
II4	δ^c	3.21	δ^m 7.34	7.13		7.13	7.34
II4	J^f	21.2	J^h 8.79	8.79		8.79	8.79
II4			J^l 5.87				5.87
III25	δ^e	3.36	δ^n	7.28	7.76		7.80
III25	J^f	21.2	J^h	9.03	8.53		
III25			J^l		5.45		7.10
III36	δ^c	3.71	δ^o 7.23		7.07	7.88	
III36	J^f	22.4	J^h 9.83		8.55	8.76	
III36			J^l			6.00	
III34	δ^c	3.26	δ^p 7.16			7.68	7.30
III34	J^f	22.0	J^h 9.83			9.82	9.82
III43	δ^c	3.30	δ^q 7.74			7.25	7.46
III43	J^f	20.5	J^h			9.40	8.79
III43			J^l 6.84				5.87
III25	$\Delta\delta$	0.09		0.10	0.41		0.42
III36	$\Delta\delta$	0.49	0.24		0.16	0.65	
III34	$\Delta\delta$	0.04	0.17			0.45	0.25
III43	$\Delta\delta$	0.09	0.40			0.12	0.12

[a] CH_2/Hi signal area ratios = 2 for i = 2, 3, 4, 5 or 6 in each compound n.m.r. spectrum; ring protons numbered as the bonded carbons in Figure 1.

[b] Omitted coupling constants could not be picked out or assigned due to the complex multiplicity and/or overlap of signals arising from the resonance of different protons.

[c] $\Delta\delta = \delta_{III_i} - \delta_{II_i}$, δ_{III_i} and δ_{II_i} = chemical shifts for the same proton in the product and in the parent compound respectively.

[d] Compound; key to legends in Figure 1.

[e] Doublet.

[f] $^2J(PH)$.

[g] Two triplets for H3 and H5 with overlap of inner peaks, and two triplets for H4 and H6 with overlap of inner peaks, each triplet showed additional splitting ($J \leq 3$ Hz).

[h] Ortho HH and/or FH coupling constant.

[i] Broad triplet of triplets for H4, broad doublet of quartets for H2, broad doublet for H6, broad quartet for H5; $J \leq 3$ Hz omitted.

[l] Meta FH coupling constant.

[m] Broad triplet for H3 and H5; broad multiplet showing 7 resonance lines for H2 and H6.

[n] Triplet for H3, multiplet containing c. 9 lines for H4 and doublet of triplets for H6; $J \leq 3$ Hz omitted.

[o] Triplet of triplets for H4, doublet of triplets for H2, doublet of doublets for H5.

[p] Broad doublet showing additional splitting for H2, broad doublet of triplets for H6 with upfield outer peak covered by the H2 signal from **III36**, broad triplet for H5; $J \leq 3$ Hz omitted.

[q] Triplet for H5, multiplet of 8 lines for H6 and doublet of triplets for H2; $J \leq 3$ Hz omitted.

quaternary carbon, three aromatic (H)C and one PCH_2 resonance signals for compounds **III**.

Compounds (**II**) were shown by TGA to be thermally stable up to 200°C; DSC scans for these compounds contained well defined endothermic peaks (Table III),

TABLE II

^{13}C magnetic resonance data for diethyl fluorobenzylphosphonates (**I**),[a] fluorobenzylphosphonic acids (**II**) and fluorobenzylphosphono-sulphonic acids (**III**)[b]: experimental chemical shifts (δ_f, p.p.m.) and coupling constants (J, Hz)[c] from ^{1}H noise-decoupled spectra

		^{13}C magnetic resonance data						
		ring carbons[e]						
Cpd[d]		C1	C2	C3	C4	C5	C6	PCH_2
I2	δ^{f}	120.3	161.4	115.6	129.1	124.5	132.6	26.4
I2	J(PC)	9.2	7.5	3.1	3.5	3.5	5.3	139.4
I2	J(PC)	15.6	245.2	22.2	8.0	8.5	2.8	
II2	δ^{f}	121.2^{f}	162.2^{f}	117.0	130.5	126.0	133.4	29.0
II2	J(PC)	10.0	7.6	3.0	3.0	≤3.1	4.6	134.3
II2	J(PC)	16.0	244.0	21.3	7.0	≤3.1	4.6	
III25	δ^{f}	122.4^{f}	163.8^{f}	117.8	128.3	140.4^{f}	131.0	29.1
III25	J(PC)	9.1	7.6			≤3.1	≤3.1	134.0
III25	J(PC)	16.8	250.2	22.4	9.2	≤3.1	≤3.1	
I3	δ^{f}	135.9	117.2	163.3	113.8	130.4	126.4	33.5
I3	J(PC)	8.8	6.6	3.2	3.5	2.9	7.0	137.0
I3	J(PC)	8.1	2.0	244.0	21.1	8.5	2.8	
II3	δ^{f}	136.6^{f}	117.9	164.1^{f}	115.2	131.8	127.1	35.6
II3	J(PC)	9.1	6.1		3.0		≤3.1	132.7
II3	J(PC)	7.6	21.4	244.1	21.4	6.1	≤3.1	
III36	δ^{f}	134.8^{f}	115.7	165.2^{f}	120.2	131.8	139.3^{f}	32.9
III36	J(PC)	9.1	3.1	3.2	4.6	8.6	8.5	131.0
III36	J(PC)	9.1	22.9	253.3	22.9	11.4	5.7	
III34	δ^{f}	140.6^{f}	119.7	160.6^{f}	134.1^{f}	130.2	127.2	35.7
III34	J(PC)	9.1				≤6.1	≤6.1	134.3
III34	J(PC)	9.1	26.0	250.2	13.0	≤6.1	≤6.1	
I4	δ^{f}	129.1	132.1	115.5	162.3	115.5	132.1	32.8
I4	J(PC)	8.8	6.8	2.9	3.8	2.9	6.8	137.6
I4	J(PC)	3.2	7.9	21.5	243.4	21.5	7.9	
II4	δ^{f}	129.9^{f}	132.8	116.9	163.2^{f}	116.9	132.8	34.9
II4	J(PC)	9.2	7.6	3.0	4.0	3.0	7.6	132.8
II4	J(PC)	3.0	7.6	21.0	243.0	21.0	7.6	
III43	δ^{f}	130.5^{f}	130.9	131.4^{f}	159.4^{f}	118.7	136.5	34.9
III43	J(PC)	9.1	≤6.1	2.3	4.5		≤2.1	133.0
III43	J(PC)	3.1	≤6.1	15.2	250.2	22.9	≤2.1	

[a] Data from Reference 9.

[b] Products of reactions (2, 4 and 6) identified after analysis of Table IV and V data: the spectrum of the product of reaction (4) contained the signals of both **III36** and **III34**; the spectra of the products of reaction (2) and (6) contained respectively only the signals of **III25** and of **III43**.

[c] Resonance bands appeared as follows: a doublet of doublets, when both J(PC) and J(FC) are given, and for $J(PC) \neq J(CF)$; a triplet, for $J(PC) = J(CF)$; a doublet, for J values preceded by ≤ to indicate that the measured value is assigned either to PC or to FC coupling and the other coupling constant is equal or lower; a doublet, and no further splitting being observed, when only J(CF) is given.

[d] Compound; key to legends in Figure 1.

[e] Carbons numbered as Figure 1.

[f] Quaternary carbons identified from ^{1}H noise-coupled ^{13}C spectra.

which were confirmed to be due to melting by visual observation in a Büchi melting-point apparatus. On the contrary, the sulphonated products **III** exhibited continuous and substantial weight loss in the same temperature range. Elemental analyses for **III** (see Experimental) supported the monohydrated fluorobenzylphosphono-sulphonic acid formula. Weight loss corresponding to the amount of water (6.25% w/w) calculated from the empirical formula occurred at 85°C for **III25**, 115°C for

TABLE III

Thermal analysis data for fluorobenzylphosphonic acids and their sulphonated products

Compound[a]	Weight loss (% w/w) from 40 to 200°C	Heat flow by DSC	
		endo/exo[b]	T (°C)[c]
II2	1.1	endo	171
II3	0.0	endo	148
II4	0.0	endo	176
III25	28.4	endo	110, 182
III36 + **III34**	11.0	endo	88
III43	17.4	exo	74, 143

[a] Key to legends as in Figure 1.
[b] Endothermal/exothermal.
[c] Temperature of maximum heat flow.

III43 and 129°C for the product containing both **III36** and **III34**. Total weight losses at 200°C (Table III) exceeded by two or four times the amount of water calculated from elemental analysis. DSC scans for these compounds exhibited poorly defined heat flow patterns, containing very broad and low intensity bands over the temperature range in which weight loss occurs. No definite melting points could be assessed by visual observation in a Büchi melting-point apparatus: a liquid phase appeared already at 40–50°C and coexisted with the solid phase, until at 180–200°C all solid phase liquified. The data certainly suggest the occurrence of thermal degradation reactions to volatile products. No further investigation was carried out on thermal behavior.

Products identification by ^1H n.m.r. spectroscopy appeared difficult. Resonance signals were very complex multiplets due to HH, FH and PH coupling. Structures were more easily assigned from ^{13}C n.m.r. spectra. For each crude product obtained from reactions (1, 3 and 5), the ^{13}C spectra were consistent with the presence of one compound. The resonance signals were assigned to the isomers **II2**, **II3** and **II4** (Table II), well in agreement with the data published for the parent isomers **I2**, **I3** and **I4** respectively.[9] For the products of reactions (2, 4 and 6), the signals assignment was more complex. In this case, the SO_3H substituent was expected to affect significantly the carbon resonances, and in addition several isomers could in principle be obtained: i.e. **III2i**, i = 3, 4, 5 and 6, from **II2**; **III3i**, i = 2, 4, 5 and 6, from **II3**; **III4i**, i = 2 and 3, from **II4**. Data were therefore elaborated in several steps (details given in Experimental Section): i.e. identification of quaternary carbon signals in the experimental resonance spectra, calculation of ^{13}C resonance chemical shifts and expected FC and PC coupling constants for each of the above product isomers, fitting of experimental to expected resonance data (Table IV), and evaluation of the degree of fitting (Table V) for each structure from the variance estimate (s^2) of the differences (Δ) between calculated (δ_{cld}) and experimental (δ_f) chemical shifts. Data appeared and were processed as follows.

The ^1H noise-coupled and ^1H noise-decoupled ^{13}C spectra of the product obtained from **II2** were consistent with the presence of one compound, i.e. three quaternary carbon signals at 122.4, 163.8 and 140.4 p.p.m., three aromatic (H)C signals at 117.8, 128.3 and 131.0 p.p.m., and one signal at 29.1 p.p.m. for the aliphatic carbon bonded to phosphorus, $(P)C(H)_2$. Comparison of the experimental (i.e. J_f for **III25**

TABLE IV

^{13}C calculated chemical shifts (δ_{cld}, p.p.m)[a] and expected coupling constants ($J(PC)_{ex}$ and $J(FC)_{ex}$, Hz)[b] for the possible product isomers (**III**) in the monosulphonation of **II**, and fitted experimental chemical shifts (δ_f, p.p.m.)[c]

Cpd[d]		ring carbons[e]					
		C1	C2	C3	C4	C5	C6
III[f]	$J(PC)_{ex}$	9.1	7.1	3.1	3.7	3.2	6.1
III[f]	$S_{J(PC)ex}$	0.5	1.0	0.4	0.3	0.4	0.7
III2[g]	$J(FC)_{ex}$	20.5	244.2	20.5	7.2	3.2	7.2
III2[g]	$S_{J(FC)ex}$	2.8	0.9	2.8	2.0	0.4	2.0
III23	δ_{cld}	122.3	159.8	131.9	128.1	127.1	137.0
III23	δ_f	122.4[h]	163.8[h]	117.8	128.3	131.0	140.4[h]
III24	δ_{cld}	124.8	163.3	114.6	145.4	123.6	134.5
III24	δ_f	122.4[h]	163.8[h]	117.8	140.4[h]	128.3	131.0
III25	δ_{cld}	122.3	165.8	118.1	128.1	140.9	131.0
III25	δ_f	122.4[h]	163.8[h]	117.8	128.3	140.4[h]	131.0
III26	δ_{cld}	118.8	163.3	120.6	131.6	123.6	148.3
III26	δ_f	122.4[h]	163.8[h]	117.8	131.0	128.3	140.4[h]
III4[i]	$J(FC)_{ex}$	3.2	7.2	20.5	244.2	20.5	7.2
III4[i]	$S_{J(FC)ex}$	0.4	2.0	2.8	0.9	2.8	2.0
III42	δ_{cld}	127.5	147.7	114.5	164.3	120.5	133.9
III42	δ_f	130.5[h]	136.5	118.7	159.4[h]	131.4[h]	130.9
III43	δ_{cld}	131.0	130.4	131.8	160.8	118.0	136.4
III43	δ_f	130.5[h]	130.9	131.4[h]	159.4[h]	118.7	136.5
III3[l]	$J(FC)_{ex}$	7.2	20.5	244.2	20.5	7.2	3.2
III3[l]	$S_{J(FC)ex}$	2.0	2.8	0.9	2.8	2.0	0.4
III32	δ_{cld}	134.2	132.8	161.7	116.3	135.4	128.2
III32	δ_f[m]	134.8[h]	120.2	165.2[h]	115.7	139.3[h]	131.8
III34	δ_{cld}	140.2	119.0	161.7	130.1	129.4	128.2
III34	δ_f[n]	139.3[h]	115.7	165.2[h]	120.2	134.8[h]	131.8
III35	δ_{cld}	137.7	121.5	165.2	112.8	146.7	124.7
III35	δ_f[m]	134.8[h]	120.2	165.2[h]	115.7	139.3[h]	131.8
III36	δ_{cld}	134.2	119.0	167.7	116.3	129.4	142.0
III36	δ_f[m]	134.8[h]	120.2	165.2[h]	115.7	131.8	139.3[h]
III32	δ_{cld}	134.2	132.8	161.7	116.3	135.4	128.2
III32	δ_f[m]	140.6[h]	134.1[h]	160.6[h]	119.7	130.2	127.2
III34	δ_{cld}	140.2	119.0	161.7	130.1	129.4	128.2
III34	δ_f[n]	140.6[h]	119.7	160.6[h]	134.1[h]	130.2	127.2
III35	δ_{cld}	137.7	121.5	165.2	112.8	146.7	124.7
III35	δ_f[n]	140.6[h]	134.1[h]	160.6[h]	119.7	130.2	127.2
III36	δ_{cld}	134.2	119.0	167.7	116.3	129.4	142.0
III36	δ_f[n]	140.6[h]	134.1[h]	160.6[h]	119.7	127.2	130.2

[a] Calculation shown in Experimental Section.

[b] Coupling constant values calculated as means of literature observations[9] in the Experimental Section; S_{jex} reported in the Table below J_{ex} values are the estimated standard deviations around the mean.

[c] Chemical shift pattern fitted to **III2i** (i = 3–6) was recorded in the n.m.r. spectrum of the product of reaction (2); pattern fitted to **III4i** (i = 2–3) was recorded in the n.m.r. spectrum of the product of reaction (6); the two patterns[m,n] recorded in the n.m.r. spectrum of the product of reaction (4), were fitted to **III3i** (i = 2, 4–6). Experimental coupling constants, J(PC) and J(FC), are reported in Table II; J values for compounds **III2i** (i = 3–6) as reported for **III26**, J values for **III3i** (i = 2, 4–6) as reported for **III35**, J values for **III4i** (i = 2–3) as reported for **III43** at the corresponding δ_f value.

[d] Compound; key to legends in Figure 1.

[e] Numbered as Figure 1.

[f] All compounds **III**.

[g] All compounds **III2i** (i = 3–6).

[h] Quaternary carbon.

[i] All compounds **III4i** (i = 2–3).

[l] All compounds **III3i** (i = 2, 4–6).

[m] Data for the main resonance pattern.

[n] Data for the lower intensity resonance pattern.

in Table II) to the expected (J_{cx} for **III** and **III2** in Table IV) coupling constants allowed to assign the two quaternary carbon signals at 122.4 and 163.8 p.p.m., and the (H)C signals at 117.8 p.p.m. to (PCH_2)C1, (F)C2, (H)C3 respectively. The remaining quaternary (S)C resonance signal at 140.4 p.p.m. and the (H)C signal at 128.3 and 131.0 p.p.m. could not unequivocally be assigned based on J values. These signals were therefore assigned to the other three ring carbons based on fitting the experimental chemical shifts to the closest calculated values (Table IV). Structure **III23** appeared already ruled out by sulphur being bonded to C4, C5 or C6. Comparison of s^2 values (Table V) calculated for **III23**, **III24**, **III25** and **III26** allows to state with confidence level (γ) $\geq$ 99% that structure **III25** fits best the experimental data.

The spectrum of the product obtained **II4** was also consistent with the presence of one compound: i.e. three quaternary carbon signals at 130.5, 159.4 and 131.4 p.p.m., three aromatic (H)C signals at 136.5, 118.7 and 130.9 p.p.m., and one (P)C$(H)_2$ signal at 34.9 p.p.m. The coupling constants (J_f for **III43** in Table II and J_{cx} for **III** and **III4** in Table IV) allowed to assign the signals at 159.4 and 130.5 p.p.m. to (F)C4 and to (PCH_2)C1 respectively. Due to the relatively large J(FC) values, the remaining quaternary carbon signal at 131.4 p.p.m. and the (H)C signal at 118.7 p.p.m. could only arise from the resonances of the carbons in ortho to

TABLE V

Mean ($\bar{\Delta}$)[a] and variance (s^2) estimates of the differences (Δ_{Ci})[b] between calculated (δ_{cld}) and experimental (δ_f) ^{13}C chemical shift for the isomers in Table IV; confidence level (γ) for the statement of variances inequality

Cpd[c]	Δ_{C1}	Δ_{C2}	Δ_{C3}	Δ_{C4}	Δ_{C5}	Δ_{C6}	$\bar{\Delta}$	s^2
III23	−0.1	−4.0	14.1	−0.2	−3.9	−3.4	0.4	48.12
III24	2.4	−0.5	−3.2	5.0	−4.7	3.5	0.4	14.91
III25	−0.1	2.0	0.3	−0.2	0.5	0.0	0.4	0.67
III26	−3.6	−0.5	2.8	0.6	−4.7	7.9	0.4	20.97
III42	−3.0	11.2	−4.2	4.9	−10.9	3.0	0.2	50.62
III43	0.5	−0.5	0.4	1.4	−0.7	−0.1	0.2	0.59
III32[d]	−0.6	12.6	−3.5	0.6	−3.9	−3.6	0.3	39.89
III34[d]	0.9	3.3	−3.5	9.9	−5.4	−3.6	0.3	32.73
III35[d]	2.9	1.3	0.0	−2.9	7.4	−7.1	0.3	24.65
III36[d]	−0.6	−1.2	2.5	0.6	−2.4	2.7	0.3	4.21
III32[c]	−6.4	−1.3	1.1	−3.4	5.2	1.0	−0.6	16.21
III34[c]	−0.4	−0.7	1.1	−4.0	−0.8	1.0	−0.6	3.42
III35[c]	−2.9	−12.6	4.6	−6.9	16.5	−2.5	−0.6	102.41
III36[c]	−6.4	−15.1	7.1	−3.4	2.2	11.8	−0.6	94.52

Statement	γ (%)
$s^2_{(III24)} = s^2_{(III23)} = s^2_{(III26)} > s^2_{(III25)}$	≥ 99
$s^2_{(III42)} > s^2_{(III43)}$	≥ 99
${s^2_{(III34)}}^d = {s^2_{(III32)}}^d = {s^2_{(III35)}}^d = {s^2_{(III36)}}^d$	≥ 95
${s^2_{(III35)}}^c = {s^2_{(III36)}}^c > {s^2_{(III32)}}^c$	≥ 95
${s^2_{(III35)}}^c = {s^2_{(III36)}}^c > {s^2_{(III34)}}^c$	≥ 99
${s^2_{(III32)}}^c > {s^2_{(III34)}}^c$	≥ 90

[a] $\bar{\Delta} = 1/6 \Sigma_{i=1}^{6} \Delta_{Ci}$.

[b] $\Delta_{Ci} = (\delta_{cld} - \delta_f)_{Ci}$, $1 \leq i \leq 6$.

[c] Compounds as in Table IV.

[d] δ_f values in the main signal pattern of the product of reaction (4).

[c] δ_f values in the minor signal pattern of the product of reaction (4).

(F)C4. The other two (H)C signals at 130.9 and 136.5 p.p.m. were therefore due to the resonances of C2 and C6. Final assignments of the above last four signals to C3 or C5, and to C2 or C6, were based on chemical shifts fitting (Table IV). Sulphur bonded to C3 or C5 rules out structures **III42** or **III46**. Comparison of s^2 values calculated for **III43** and **III42** (Table V) confirmed this conclusion with $\gamma \geq 99\%$.

The spectrum of the product obtained from **II3** contained a main pattern of 6 aromatic carbon resonance signals (i.e. three quaternary carbon signals at 134.8, 165.2 and 139.3 p.p.m., and three (H)C signals at 115.7, 120.2 and 131.8 p.p.m.) and a lower intensity pattern of six other signals (i.e. three quaternary carbon signals at 140.6, 160.6 and 134.1 p.p.m., and three (H)C signals at 119.7, 130.2 and 127.2 p.p.m.). Coherently, two $(P)C(H)_2$ signals were also present; these signals had chemical shifts of 32.9 and 35.7 p.p.m. and 1:0.2 relative area ratios. The presence of two compounds was confirmed by ^{31}P and ^{19}F: i.e. two ^{31}P resonance signals at 25.3 and 25.0 p.p.m. with 1:0.2 relative area ratio and two ^{19}F resonance signals at −41.18 and −35.3 p.p.m. with 1:0.14 relative area ratios. None of these signals was due to the parent compound **III3**, as assessed on comparing the product and the parent compound spectra. For the main ^{13}C resonance signals pattern of the product obtained from **II3**, and based on FC coupling constants (J_f for **III36** in Table II and J_{cx} for **III** and **III3** in Table IV), the signal at 165.2 p.p.m. could unequivocally be assigned to (F)C3, the signals at 120.2 and 115.7 p.p.m. were clearly arising from the resonances of the carbons in ortho to (F)C3, and the other signals were to be assigned to C1, C5 and C6. Sulphur could only be bonded to C5 or C6, and this rules out structures **III32** and **III34**. Final assignments were based on chemical shifts fitting (Table IV). Comparison of s^2 values (Table V) calculated for **III32**, **III34**, **III35** and **III36** shows structure **III36** as the best fitting with $\gamma \geq 95\%$.

For the low intensity ^{13}C resonance signals pattern in the spectrum of the product obtained from **II3**, the coupling constants (J_f for **III34** in Table II and J_{cx} for **III** and **III3** in Table III) allow to assign the signals at 140.6 and 160.6 p.p.m. to $(PCH_2)C1$ and (F)C3 respectively. The signal at 119.7 p.p.m. was assigned to C2 or C4, due to its relatively large J(FC) constant. The signals at 130.2 and 127.2 p.p.m. had small J constants, fitting better the values expected for C5 and C6 resonances. The quaternary (S)C resonance signal at 134.1 p.p.m. was therefore assigned to one of the carbons in ortho to (F)C3, even if its J(FC) value was lower than that expected. Sulphur bonded to one of these two ring carbons rules out structures **III35** and **III36**. Relative assignments of the above last four signals (i.e. to C2 or C4, and to C5 or C6) were based on chemical shifts fitting (Table IV). Comparison of s^2 values (Table V) calculated for **III32**, **III34**, **III35** and **III36** allows to state with $\gamma \geq 95\%$ that the two structures with sulphur bonded to C2 or C4 fit the experimental data better than **III35** and **III36**. Comparison of s^2 values for **III32** and for **III34** indicates the latter to fit better the experimental data, but the confidence level for this statement ($90\% \leq \gamma < 95\%$) results lower than in the other cases above.

^1H n.m.r. spectra were tentatively analyzed and interpreted as shown in Table I, based on the structures assigned by ^{13}C n.m.r. spectroscopy. The ^1H spectra contained resonance bands with splitting of proton absorption appearing at three levels, i.e. 8–10 Hz due to ortho HH and FH coupling, 5–7 Hz due to meta FH coupling, and ≤3 Hz possibly due to meta and para HH coupling, and to PH coupling. The order of assigned chemical shifts is in agreement with the nature of the substituents.[11] For the parent compounds **II**, the order of deshielding for protons bonded to carbons in ortho (o-), para (p-) and meta (m-) to the carbon bonded to fluorine is o- < p- < m-, as expected for an ortho-para orienting substituent. Sulphonation shifts the resonance of all ring protons downfield, but the magnitude of the effect ($\Delta\delta$ in Table I) varies over the ring. The protons in ortho to SO_3H experience the strongest deshielding effect, as expected for a meta orienting substituent. It should also be observed that deshielding is shown also for the CH_2P protons, the highest effect being observed in **III36** where the SO_3H and CH_2P substituents are adjacent. Analysis of ^{31}P and ^{19}F spectra did not allow any better structural assessment.

All together the data are worth some comments regarding the course of the reaction. The product yields and rate of formation show that, although the two substituents in **II** are both expected to deactivate the ring, the electrophilic substitution at the aromatic carbons by the SO_3H group still occurs with fast kinetics at room temperature. Examination of the nature and distribution of the sulphonated isomers, and of the nature of the parent compounds, shows that orientation of the entry of the third substituent in the aromatic ring seems ruled largely by the ortho-para mesomeric effect of fluorine. Compound **II3** yields in fact the isomers with the SO_3H substituent in para and in ortho to fluorine. Compound **II4** yields selectively only the isomer with the $-SO_3H$ in ortho to fluorine, the para position being occupied by the CH_2P substituent. Compound **II2** yields selectively the isomer with the SO_3H substituent in para to fluorine. In compounds **III43** and **III25**, the SO_3H substituent happens to be in meta to the CH_2P substituent, which in this case may also contribute to determine the position of entry of the third substituent. Consistently with this argument, in the case of compound **II2**, substitution at C3 could be expected, since this carbon is both in ortho to fluorine and in meta to the CH_2P substituent. Failure for this to occur may be due to steric factors.

EXPERIMENTAL

Reagents. Triethyl phosphite was purchased from Fluka. 2-fluoro-, 3-fluoro-, and 4-fluorobenzylbromide were purchased from Aldrich. All other reagents were C. Erba RPE products. Liquid SO_3 was distilled from 20% oleum and handled as previously reported.[1] Diethyl benzylphosphonates (i.e. the ortho, meta and para isomer) were obtained according to previous work.[9] All materials were used without any further purification.

Physical Measurements. TGA and DSC scans were performed by DuPont 2000 and by Mettler TA 4000 instruments, in N_2 at 100 mL/min, from ambient to 220°C at 10°C/min. ^1H (at 399.8 MHz), ^{13}C (at 100.5 MHz), ^{31}P (at 161.8 MHz) and ^{19}F (at 376.2 MHz) n.m.r. spectra were recorded in D_2O at room temperature on Jeol EX 400 spectrometer. The sample concentration in D_2O was ca. 10% w/w. ^1H and ^{13}C chemical shifts (δ^1H and $\delta^{13}C$) were measured in p.p.m. from internal 1% w/w 2-methyl-2-propanol (MP) and converted into values referred to TMS by adding, to the measured ^1H and ^{13}C values, 1.29 and 31.30 p.p.m. respectively for the ^1H and ^{13}C chemical shifts of the methyl group in MP from TMS. ^{31}P chemical shifts ($\delta^{31}P$) are in p.p.m. from external 85% w/w H_3PO_4 in D_2O. ^{19}F chemical shifts ($\delta^{19}F$) are in p.p.m. from external pure CF_3COOH.

Chemical Analyses. C, H and S concentrations were obtained by C. Erba 1108 elemental analyzer. F and P were determined[12] respectively by titration with thorium nitrate and precipitation as $(NH_4)_3PO_4 \cdot 12\ M_oO_3$, after ashing the sample and separating fluoride from phosphate ions by addition of silver nitrate.

The oxygen concentration was calculated from the difference to 100 of the sum of the concentrations of the other elements above.

Calculation of ^{13}C Chemical Shifts. The chemical shifts (δ_{cld}) of the ^{13}C resonance signals for compounds **III** were calculated on the basis of the additivity of substituents effects,[13] starting from the experimental δ values of the parent phosphonic acid (Table II) and adding the SO_3H effect at each carbon, i.e. 14.9 p.p.m. at the carbon bearing the C—S bond, and −2.4, 1.1 and 3.6 at the ortho-, meta- and para-carbon respectively.

^{13}C Resonance Signals Assignment. Quaternary carbons, $(PCH_2)C$, (F)C and (S)C, and carbons bonded to hydrogen, (H)C, were identified from both ^1H noise-coupled and ^1H noise-decoupled ^{13}C resonance spectra. Assignments of experimental signals for aromatic carbons to carbons in the structure under consideration (Table IV) were accomplished by fitting first the experimental (J_f in Table II) to the expected[9] (J_{ex} in Table IV) phosphorus-carbon and fluorine-carbon coupling constants. The expected $J(PC)_{ex}$ constants were calculated as averages of 16 observations[9] recorded for diethyl benzylphosphonate, for the isomers **I2**, **I3** and **I4**, and for twelve other mono-, di- and trisubstituted diethyl benzylphosphonates. Expected $J(FC)_{ex}$ constants were calculated as averages of the data published[9] for the three fluorobenzylphosphonate isomers **I2**, **I3** and **I4**. For both $J(PC)_{ex}$ and $J(FC)_{ex}$ the estimated standard deviations $S_{J(PC)ex}$ and $S_{J(FC)ex}$ (Table IV) show that $J(FC)$ values may allow unequivocal identification of some carbon signals: i.e. for the F bonded carbon and for the carbons in ortho to it. In the cases where J values did not allow unambiguous assignment, signals were assigned based on fitting the experimental (δ_f) to the closest calculated (δ_{cld}) chemical shift. Fitting of the same experimental data pattern was performed for each of the possible product isomers obtainable in the monosulphonation of the given parent compound **II** (Table IV). Assessment of the structure best fitting the experimental data was performed by computing for each structure under consideration the average ($\bar{\Delta}$) and the variance estimate (s^2) of the differences between δ_{cld} and δ_f taken over the six ring carbons:

$$\bar{\Delta} = 1/6 \sum_{i=1}^{6} \Delta_{Ci},\ \Delta_{Ci} = (\delta_{cld} - \delta_f)_{Ci},\ 1 \leq i \leq 6.$$

$\bar{\Delta}$ values (Table V) were not significantly different from zero by Student's t-test.[14] The estimated variance indicated the degree of fitting of the experimental to the calculated chemical shifts for the structure under consideration. Comparison of s^2 values based on F distribution Tables,[14] for the structures under consideration, allowed to establish the lowest s^2 value (and thus the best fitting structure) with confidence level (γ) $\geq 95\%$, as shown in Table V.

Sulphonation of **I** *and Product Characterization.* Liquid SO_3 was added to **I** (c. 6 g) under magnetic stirring and N_2 blanketing at 0°C and at $1 \leq SO_3/I$, mole/mole ≤ 6. The resulting mixture was a viscous liquid, which was allowed to equilibrate with the room temperature, and was afterward quenched with D_2O to convert unreacted SO_3 to diluted sulphuric acid and with $CDCl_3$ to separate unreacted **I** soluble in $CDCl_3$ from the products soluble in water. The separated phases were then analyzed by n.m.r. spectroscopy; the products were identified by comparison of the resonance signals with those of authentic **I**, and of compounds **II** and **III** as reported in Tables I and II. It was found that at $SO_3/I < 3.0$ the reaction mixtures contained both **I** and the corresponding sulphonated product isomer shown in Figure 1. At $3.0 \leq SO_3/I \leq 6.0$, **I** was absent; the reaction mixtures contained **II**, deriving from the hydrolysis of unsulphonated **I** by D_2O, **III** and 2-hydroxyethanesulphonic acid (two triplets with $J(HH) = 6.5$ Hz, and $\delta = 3.26$ p.p.m. for H_2CS and 4.31 p.p.m. for H_2CO).

Preparation of Compounds **II**. **I** (c. 10 g) was refluxed with 100 ml concentrated HCl until a clear solution was obtained. The solution, concentrated in a rotary vacuum evaporator, yielded a precipitate which was recovered (c. 7 g) by filtration and washed with n-pentane. The product was identified from its ^1H (Table I) and ^{13}C (Table II) n.m.r. spectrum and characterized by TGA and DSC scans (Table III).

Sulphonation of Compounds **II**. The reaction between fluorobenzylphosphonic acid and SO_3 was carried out at 3.2 SO_3/III mole ratio as described above. The reaction mixture was quenched with H_2O. The sulphonic acids were separated from H_2SO_4 by a previously established procedure[1,2]: i.e. addition of $HCl/BaCl_2$, filtration of insoluble $BaSO_4$, removal of soluble excess Ba^{2+} by ion exchange, and drying under vacuum at 60°C. Weighing and analysis of the residue by n.m.r. spectroscopy demonstrated occurrence of reactions 2, 4 and 6 (Figure 1) with nearly quantitative mole/mole yield. The raw products were viscous liquids which crystallized upon long standing in the stoppered evaporation flash at room temperature. Elemental analysis data for the solid products gave the following results: for the product obtained from **II2**, C 29.05, H 3.67, F 6.40, P 11.57, S 11.41 and O 37.90% w/w, corresponding to C 6.8, H 10.2, F 0.95, P 1.0, S 1.0 and O 6.7 relative atom/atom ratios; for the product obtained from **II3**, C 28.76, H 3.35, F 6.10, P 11.84, S 11.56 and O 38.39% w/w, corresponding to C 6.7, H 9.2, F 0.89, P 1.1, S 1.0 and O 6.7 atom/atom; for the product obtained from **II4**, C 27.82, H 3.61, F 6.45, P 10.72, S 11.25 and O 40.15% w/w, corresponding to C 6.6, H 10.2, F 0.97, P 0.99, S 1.0 and O 7.1 atom/atom. The data fit the theoretical formula for monohydrated fluorobenzylphosphono-sulphonic acid, $C_7H_{10}FO_7PS$: C 29.17, H 3.50, F 6.59, P 10.74, S 11.12 and O 38.36% w/w.

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