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POLYFLUORO-HETEROCYCLIC COMPOUNDS—XIII[1]

PREPARATION AND NUCLEOPHILIC SUBSTITUTION REACTIONS OF POLYFLUORO-2,2′-BIPYRIDYLS

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Abstract—Octachloro-2,2′-bipyridyl can be obtained in high yield from the reaction between 2,2′-bipyridyl and phosphorus pentachloride at elevated temperatures. Replacement of chlorine for fluorine in octachloro-2,2′-bipyridyl is difficult; it occurs using anhydrous potassium fluoride but is more effective using sulpholan as solvent. Low yields of octafluoro-, 3-chloroheptafluoro-, 3,3′-dichlorohexafluoro-, and 3,3′,5-5′-tetrachlorotetrafluoro-2,2′-bipyridyl are obtained. These polyfluoro-2,2′-bipyridyls have been shown to undergo nucleophilic substitution reactions with sodium methoxide leading to exclusive replacement of the fluorine atoms para to the ring nitrogen.

IN PREVIOUS papers in this series, we have described the synthesis and some of the nucleophilic substitution reactions of various polyfluoro aromatic nitrogen heterocyclic compounds. We have shown that one of the most convenient methods of preparing highly fluorinated aromatic nitrogen heterocycles has been the replacement of chlorine in highly chlorinated compounds by fluorine, using potassium fluoride at elevated temperatures.[2,3] We now report attempts to extend this halogen exchange reaction to the synthesis of highly fluorinated 2,2′-bipyridyls from octachloro-2,2′-bipyridyl.

Based on the early work of Sell and Dootson,[4] recent work[2,5] has shown that highly chlorinated heterocyclic compounds can be obtained in high yield by reacting the heterocycle with phosphorus pentachloride at elevated temperatures. Under similar conditions to those reported for the synthesis of pentachloropyridine, octachloro-2,2′-bipyridyl has been prepared in high yield. The results of this chlorination reaction with 2,2′-bipyridyl are shown in Table 1.

The formation of pentachloropyridine indicates that some dissociation into pyridyl radicals occurs under these conditions the latter then abstracting a chlorine atom from phosphorus pentachloride. In each reaction small amounts of lower chlorinated 2,2′-bipyridyls were isolated which were rechlorinated in separate reactions to give octachloro-2,2′-bipyridyl. It has been noted previously that partly chlorinated nitrogen heterocycles are very efficiently converted to the perchloro derivatives.[2]

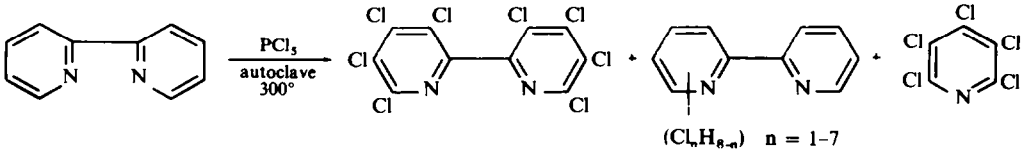
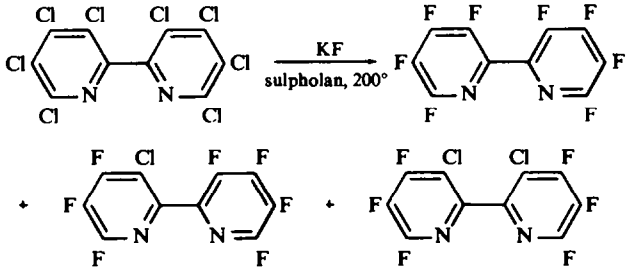


TABLE 1. CHLORINATION OF 2,2'-BIPYRIDYL WITH PHOSPHORUS PENTACHLORIDE

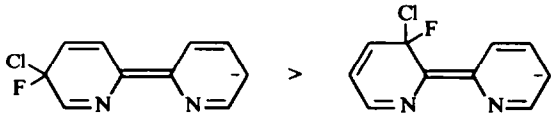
Reaction	Wt of PCl_5 (g)	Wt of $C_{10}H_8N_2$ (g)	Time (hr)	Temp (°)	Wt of chlorinated products (g)	Mole-% C_5Cl_5N	Composition of product	
							$C_{10}H_nCl_{(8-n)}N_2$ (n = 1–7)	$C_{10}Cl_8N_2$
1	500	20	12	300	10·8	35	25	40
2	2000	40	12	300	101	3	2	95
3	2500	50	12	300	123	5	5	90

In a single reaction between octachloro-2,2′-bipyridyl and anhydrous potassium fluoride in the absence of solvent at 300°, the main product was 3,3′,5,5′-tetrachlorotetrafluoro-2,2′-bipyridyl together with small amounts of more highly fluorinated material. When the temperature was increased, only decomposition resulted indicating the decreased stability of the fluorinated or chlorinated 2,2′-bipyridyls with respect to the corresponding perhalo pyridines or quinolines the latter being formed at temperatures up to 480°. When the reaction between octachloro-2,2′-bipyridyl and potassium fluoride was carried out using sulpholan as solvent at 200°, octafluoro-, 3-chloroheptafluoro-, and 3,3′-dichlorohexafluoro-2,2′-bipyridyl were isolated together with small amounts of lower fluorinated material. The results of these and other reactions performed during the investigation are summarized in Tables 2 and 3.

The chlorine atoms ortho and para to the ring nitrogens are obviously more easily replaced than those in the meta position and this result is consistent with the results obtained from the fluorination of pentachloropyridine[2,5] using potassium fluoride. It is also evident that the chlorine atoms in the 5 and 5′ positions are more readily replaced than those in the 3 and 3′ positions as no mixture of isomers of the monochloroheptafluoro- or the dichlorohexafluoro-2,2′-bipyridyls is formed. It is suggested



that the enhanced reactivity at the 5 and 5′ positions relative to the 3 and 3′ positions (which are both meta to the ring nitrogen) is due to the fact that when nucleophilic attack takes place at the 5 position the transition state is stabilized by delocalization of charge throughout the ring system (I). Stabilization of the transition state can take place when nucleophilic substitution takes place at the 3 position, but it appears that activation of para positions by substituent groups is much more effective than orthoactivation in polyfluoroaromatic systems (II).[6]



I II

Some ortho-activation is, nevertheless, evident from the isolation of octafluoro-2,2′-bipyridyl, using potassium fluoride in sulpholan, since the 3- and 5-chlorines in pentachloropyridine are not replaced using this system.[2]

It has been shown that pentafluoropyridine reacts with various nucleophilic reagents to replace, almost exclusively, the fluorine atom in the 4 position,[7,8] and

TABLE 2. REACTIONS OF OCTACHLORO-2,2′-BIPYRIDYL WITH POTASSIUM FLUORIDE IN THE ABSENCE OF A SOLVENT

Reaction	Wt of KF (g)	Wt of $C_{10}Cl_8N_2$ (g)	Temp (°)	Time (hr)	Product (g)	Composition of product in mole-% (% yield in parentheses)			
						$C_{10}Cl_4F_4N_2$	$C_{10}Cl_2F_6N_2$	$C_{10}ClF_7N_2$	$C_{10}F_8N_2$
1	50(KF)	4	460	17	—	Decomposition			
2	50(KF)	4	400	17	—	Decomposition			
3	9(KF)	0·94	355	15	trace				
4	15(KF)	2	340–346	16·25	0·2	10(1·2)	40(5·2)	trace	trace
5	15(KF)	3	296–316	16·25	2·1	90(74·7)	trace	trace	

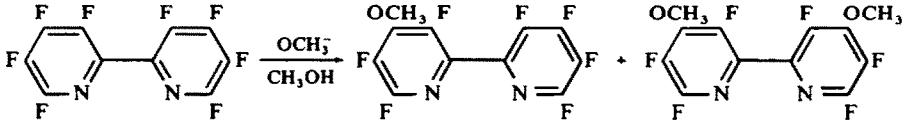
The product from reaction 4 contained another product (50%) which was thought to be 3,3′,5,-trichloropentafluoro-2,2′-bipyridyl.
The product from reaction 5 contained 10% of this trichloropentafluoro-2,2′-bipyridyl.

TABLE 3. REACTIONS OF OCTACHLORO-2,2′-BIPYRIDYL WITH POTASSIUM FLUORIDE IN SULPHOLAN

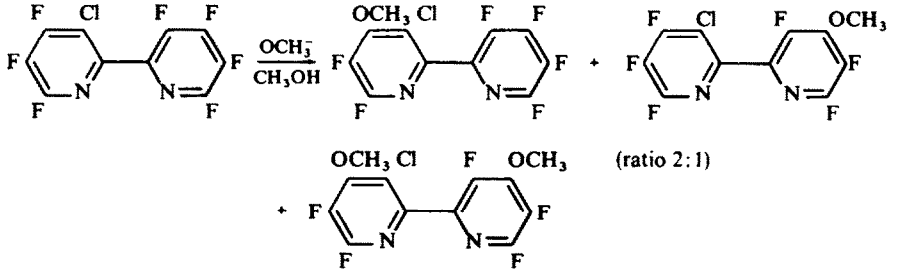
Reaction	Wt of KF (g)	Wt of $C_{10}Cl_8N_2$ (g)	Temp (°)	Time (hr)	Product (g)	Composition of product in mole % (% yield in parentheses)		
						$C_{10}Cl_2F_6N_2$	$C_{10}ClF_7N_2$	$C_{10}F_8N_2$
1	15	5	140	6	0·8	40(8·3)	20(4·4)	35(8·1)
			200–210	16				
2	20	5	200	22·5	2·15	85(47·5)	5·8(3·9)	2·3(1·4)
3	100	20	200	15·75	8·9	63·4(36·6)	26·7(16·2)	9·9(6·3)
4	375	75	200	13·5	34·6	53·1(31·8)	32·7(20·6)	14·2(9·4)

The product from Reactions 1 and 2 contained small amounts of a compound believed to be trichloropentafluoro-2,2′-bipyridyl.

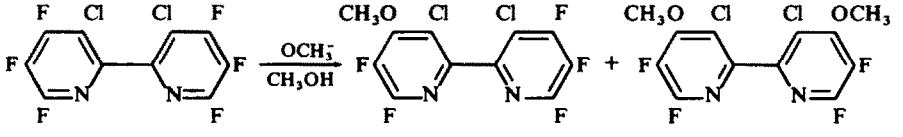
the polyfluoro-2,2′-bipyridyls react in a similar way with replacement of the fluorine atoms at the 4 and 4′ positions. Equimolar amounts of octafluoro-2,2′-bipyridyl and sodium methoxide react readily at room temperature yielding both the mono and di-substituted derivatives.



Sodium methoxide reacts with 3-chloroheptafluoro-2,2′-bipyridyl to yield a mixture of isomers of the monether together with the di-ether.



Nucleophilic replacement of fluorine in 3,3′-dichlorohexafluoro-2,2′-bipyridyl takes place at the 4 and 4′ positions, yielding the mono- and di-ethers.



NMR spectra. The orientation of the polyfluoro-2,2′-bipyridyls and their substituted derivatives were determined from NMR chemical shift-data by incorporating the known effects of substituent groups on the F^{19} chemical shifts in pentafluoropyridine and related compounds. The *ortho*, *meta* and *para* fluorine atoms in polyfluoropyridine systems are so well separated that they can be easily identified, enabling various structural possibilities to be clearly distinguished.

Octafluoro-2,2′-bipyridyl can be considered as monosubstituted- tetrafluoropyridine, therefore, if a group X in 4-X tetrafluoropyridine affects the chemical shift of the 3,5-fluorines by Z ppm, relative to the chemical shift of the same fluorine in pentafluoropyridine, then in 4-X-heptafluoro-2,2′-bipyridyl, the same effect on the chemical shift of the 3,5-fluorines relative to octafluoro-2,2′-bipyridyl can be expected.

From the F^{19} chemical shift data listed in Table 4, it is possible to calculate the chemical shifts for substituted polyfluorobipyridyls. When two substituents are present in one ring, then the combined effects of both substituents are incorporated to calculate the expected chemical shifts. In monosubstituted heptafluorobipyridyls, it appears that the substituent has little or no effect on the chemical shifts due to the fluorine atoms in the other ring. When more than one orientation is possible, the

chemical shifts have been calculated for all possible orientations while, for the sake of space, only those values for the assigned structure are given.

The assignment of the 3- and 5-fluorine chemical shifts in the spectrum of octafluoro-2,2'-bipyridyl was confirmed by reference to the chemical shifts for decafluorobiphenyl. Although it has been emphasised[9] that this type of extrapolation is only satisfactory because the differences in the observed values are so large. The relevant data from the fluorine-19 NMR spectra of polyfluoropyridines are summarized in Table 4 and the chemical shifts of the various polyfluoro-2,2'-bipyridyl are shown in Table 5, together with the calculated shifts for the structures assigned.

EXPERIMENTAL

NMR spectra were determined using an A.E.I. R.S.2 spectrometer, operating at 60 Mc/s. Samples were examined as neat liquids or as solns in acetone, with hexafluorobenzene as internal reference. The chlorination reactions were carried out using stainless steel autoclaves of 5 litre and 120 ml capacity respectively.

Chlorination of 2,2'-bipyridyl

In a typical experiment, an autoclave (5 l.) charged with 2,2'-bipyridyl (40 g, 0·26 mole) and PCl_5 (2000 g, 9·6 mole) was heated rapidly to 300° (2 hr) and then maintained at this temp for a further 10 hr. The autoclave was allowed to cool and vented to release the HCl formed during the reaction before the vessel was opened. The product was then hydrolysed by slowly adding it to ice. When this was complete, the chlorinated product was filtered off and dried (P_2O_5), after which the product was sublimed to give a white solid (101 g). Fractional sublimation afforded three main fractions:

(i) pentachloropyridine (2·0 g) m.p. 120–123° (from benzene), (lit.[9] 124–125°); (ii) a white solid (0·5 g) m.p. 175–178° which was thought to be a mixture of hexa- and heptachloro-2,2'-bipyridyls; (iii) *octachloro-2,2'-bipyridyl* (97 g, 87%) m.p. 184–187° (from benzene), (Found: C, 27·9; Cl, 65·6. $C_{10}Cl_8N_2$ requires: C, 27·8; Cl, 65·7%).

Replacement of Chlorine by Fluorine in Octachloro-2,2'-bipyridyl

(a) *Using potassium fluoride in the absence of solvent.* Octachloro-2,2'-bipyridyl (3 g, 0·007 mole) and anhyd KF (15 g, 0·26 mole) were sealed under vacuum in a Carius tube and heated to 296–316° for 16 hr. The tube was allowed to cool and the contents added to water. Then the aqueous mixture was extracted with ether and the combined extracts dried ($MgSO_4$) and ether was removed by distillation to give a clear liquid which, when distilled under reduced press, afforded a thick oil (2·1 g) that was shown by analytical VPC (silicone oil on celite at 200°) to be a mixture of two components in the ratio 9:1. Fractional distillation under reduced press gave *3,3',5,5'-tetrachloro-4,4',6,6'-tetrafluoro-2,2'-bipyridyl* (the main component of the mixture), (Found: C, 32·8; F, 20·7; Cl, 38·5. $C_{10}F_4N_2$ requires: C, 32·8; F, 20·8; Cl, 38·8%). The other components in the reaction was thought to be 3,3',5-trichloropentafluoro-2,2'-bipyridyl, but was not isolated.

(b) *Using potassium fluoride in sulpholan.* Octachloro-2,2'-bipyridyl (20 g, 0·046 mole), KF (100 g, 1·7 mole) and dry sulpholan (310 g) were vigorously stirred at 200° for 15 hr. The contents of the reaction flask were cooled to room temp, water was added, the aqueous mixture was extracted with ether, and the combined extracts washed well with water. The extracts were dried ($MgSO_4$) and the solvent removed by distillation to give a black oil (10·4 g). Distillation under reduced press, (64–70°/0·9 mm), afforded a clear oil (8·9 g) which was shown by analytical scale VPC (silicone oil on celite at 170°) to be a mixture of 3 components in the ratio 10·27:63. The three components were separated, using preparative scale VPC (silicone elastomer on celite at 160°), to give: (a) *octafluoro-2,2'-bipyridyl* (6·3%). (Found: C, 39·8; F, 50·2. $C_{10}F_8N_2$ requires: C, 40·0; F, 50·6%) as a low melting solid b.p. 223–224°; (b) *3-chloroheptafluoro-2,2'-bipyridyl* (16·2%). (Found: C, 38·0; F, 41·7; Cl, 11·8. $C_{10}ClF_7N_2$ requires: C, 37·9; F, 42·0; Cl, 11·2%) b.p. 233–234°; and (c) *3,3'-dichlorohexafluoro-2,2'-bipyridyl* (36·6%). (Found: C, 36·3; F, 33·5; Cl, 20·7. $C_{10}Cl_2F_6N_2$ requires: C, 36·04; F, 34·2; Cl, 21·3%) m.p. 45–48°.

The reaction of polyfluoro-2,2'-bipyridyls with sodium methoxide in methanol

The following general procedure was used: a 3-necked flask fitted with a dropping funnel, gas inlet

TABLE 4. FLUORINE-19 CHEMICAL SHIFTS IN DERIVATIVES OF PENTAFLUOROPYRIDINE AND DECAFLUOROBIPHENYL (POSITION OF THE FLUORINE ATOM IN PARENTHESES)

	Compound	Chemical shift from hexafluorobenzene (ppm) (+ve shifts are measured to higher field)				Group (position in parentheses)	Effect on fluorine-19 shifts ortho	meta	para	Ref. cpd.
A.	Pentafluoropyridine	−74·7(2,6);	−0·3(3,5);	−28·1(4)						
B.	4-Methoxytetrafluoropyridine	−70·0(2,6);	−1·2(3,5)			OCH_3(4)	−1	+5	—	A
C.	3-Chlorotetrafluoropyridine	−90·2(2);	−48·0(4);	1·6(5);	−76·6(6)	Cl(3)	(−16)	+2	−2	A
D.	3,5-Dichlorotrifluoropyridine	−92·4(2,6);	−68·1(4)			Cl(3,5)	(−20) (−16)	—	−2	G
E.	Decafluorobiphenyl	−24·03(0);	−1·52(m);	−12·01(p)		C_6F_5	−24	−1·5	−12	C_6F_6

TABLE 5. FLUORINE-19 CHEMICAL SHIFTS IN DERIVATIVES OF OCTAFLUOROBIPYRIDYLS
(POSITION OF THE FLUORINE ATOM IN PARENTHESES)

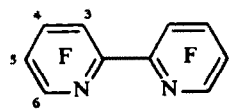
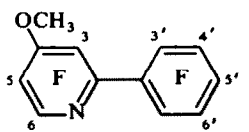
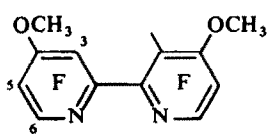
	Compound	Chemical shift from hexafluorobenzene (ppm)			Reference compound(s)
	(intensity ratio of peaks in parentheses in order of increasing value of the chemical shift from low to high field)	Measured		Calculated	(incorporating Table 4)
I	 (1:1:1:1)	−20·9	(3)	−24	E; A
		−25·4	(4)	−30	
		−9·1	(5)	−12	
		−81·2	(6)	−76	
II	 (1:1:2:1:1:1)	−23·8	(3)	−23	I; B
		−7·4	(5)	−10	
		−76·6	(6)	−76	
		−20·3	(3′)	−21	
		−23·8	(4′)	−25	
		−9·7	(5′)	−9	
		−79·7	(6′)	−81	
III	 (1:1:1)	−23·2	(3)	−24	II
		−8·4	(5)	−7	
		−76·1	(6)	−77	

TABLE 5.—*continued*

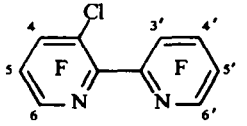
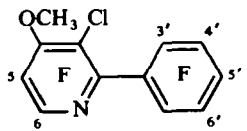
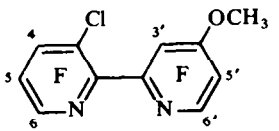
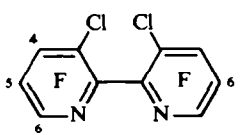
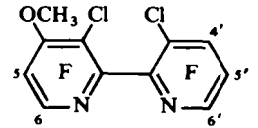
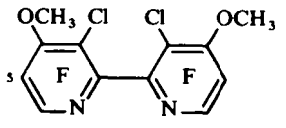
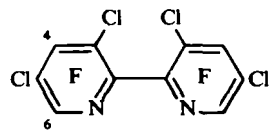
IV	 (2:1:1:1:1)		−46·1	(4)	−44	C; I
			−6·0	(5)	−7	
			−80·9	(6)	−83	
			−21·8	(3′)	−21	
			−24·9	(4′)	−25	
			−8·6	(5′)	−9	
			−80·3	(6′)	−81	
				(X)		
V		(X)	−4·3	(5)	−7	I; IV; B
			−75·6	(6)	−76	
			−19·4	(3′)	−21	
			−22·8	(4′)	−25	
			−5·3	(5′)	−9	
			−78·4	(6′)	−81	
		(Y)		(Y)		
	 (isomers in ratio 2:1 (X to Y) (3:2:1:1:3:2:1:4:1)		−44·0	(4)	−46	IV; I; B
			−3·3	(5)	−6	
			−78·4	(6)	−81	
			−22·6	(3′)	−22	
			−7·1	(5′)	−10	
			−74·8	(6′)	−76	
VI	 (1:1:1)		−45·8	(4)	−46	IV
			−5·6	(5)	−6	
			−81·4	(6)	−81	

TABLE 5.—*continued*

VII	 (1:1:1:1:1)	−6·1	(5)	−7	VI; B
		−77·1	(6)	−76	
		−44·8	(4′)	−46	
		−4·4	(5′)	−6	
		−80·3	(6′)	−81	
VIII	 (1:1)	−5·2	(5)	−6	VII
		−76·8	(6)	−77	
IX	 (1:1)	−66·7	(4)	−65	I; D
		−95·6	(6)	−98	

tap, reflux condenser, and a magnetic stirrer was flushed with dry N_2 for 30 min prior to use. During the reaction, a stream of dry N_2 was passed through the apparatus. To a stirred soln of the polyfluoro-2,2'-bipyridyl, dissolved in dry MeOH, was added, dropwise over a period of 5–30 min, at 20°, a soln of NaOMe (prepared by adding the required amount of Na to MeOH) in dry MeOH. The soln was stirred for a further 20 to 60 min and then poured into cold water. The white ppt which resulted was extracted into organic solvent (ether or CH_2Cl_2), washed well with water, dried ($MgSO_4$), and the solvent removed by distillation. The composition of the reaction product was investigated using analytical-scale gas chromatography and the products purified by preparative-scale gas chromatography.

Reaction between octafluoro-2,2'-bipyridyl and sodium methoxide

To a stirred soln of the bipyridyl (0·835 g, 0·0028 mole) dissolved in MeOH (15 ml) was added dropwise over 5 min, at 20°, a soln of Na (0·068 g, 0·003 mole) in MeOH (20 ml). The reaction soln was stirred for a further 30 min, then treated as described. The reaction products (0·81 g) were separated by preparative-scale VPC and identified as: (i) unreacted octafluoro-2,2'-bipyridyl; (ii) *4-methoxyheptafluoro-2,2'-bipyridyl* (75%). (Found: C, 42·2; H, 0·94; F, 42·0. $C_{11}H_3F_7N_2O$ requires: C, 42·3; H, 0·96; F, 42·6%), m.p. 39–40·5°; (iii) *4,4'-dimethoxyhexafluoro-2,2'-bipyridyl* (16%). (Found: C, 43·9; H, 1·76. $C_{12}H_6F_6N_2O_2$ requires: C, 44·4; H, 1·85%), m.p. 50–51°.

Reaction between 3-chloroheptafluoro-2,2'-bipyridyl and sodium methoxide

A soln of Na (0·06 g, 0·0026 mole) in MeOH (20 ml) was added, dropwise over 10 min, at 20°, to a stirred soln of the bipyridyl (0·826 g, 0·0026 mole) dissolved in MeOH (20 ml). The soln was stirred for a further 30 min, then treated as described. The reaction product (0·73 g) were separated by preparative VPC and identified as: (i) unreacted 3-chloroheptafluoro-2,2'-bipyridyl; (ii) a 2:1 molar ratio of *3-chloro-4-methoxyhexafluoro-2,2'-bipyridyl* and *3-chloro-4'-methoxyhexafluoro-2,2'-bipyridyl* (67%). (Found: C, 40·3; H, 0·95; F, 35·5; Cl, 11·0. $C_{11}H_3ClF_6N_2O$ requires: C, 40·2; H, 0·91; F, 34·7; Cl, 10·8%), b.p. (of mixture) 273–276°; and (iii) *3-chloro-4,4'-dimethoxypentafluoro-2,2'-bipyridyl* (14%). (Found: C, 41·8; H, 1·71. $C_{12}H_6ClF_5N_2O_2$ requires: C, 42·3; H, 1·76%), m.p. 72–74°.

Reaction between 3,3'-dichlorohexafluoro-2,2'-bipyridyl and sodium methoxide

A soln of Na (0·078 g, 0·0034 mole) in MeOH (20 ml) was added dropwise over 15 min, at 20°, to a stirred soln of the bipyridyl (1·12 g, 0·0034 mole), dissolved in MeOH (15 ml). The soln was stirred for a further 30 min, then treated as described. The reaction product (1·05 g) were separated by preparative GLC and identified as:

(i) *3,3'-dichloro-4-methoxypentafluoro-2,2'-bipyridyl* (68%). (Found: C, 38·1; H, 0·92; F, 27·1; Cl, 20·8. $C_{11}H_3Cl_2F_5N_1O$ requires: C, 38·26; H, 0·87; F, 27·5; Cl, 20·6%), b.p. 299–301°; and (iii) *3,3'-dichloro-4,4'-dimethoxytetrafluoro-2,2'-bipyridyl* (16%). (Found: C, 40·1; H, 1·70; F, 20·1; Cl, 19·8. $C_{12}H_6Cl_2F_4N_2O_2$ requires: C, 40·3; H, 1·68; F, 21·3; Cl, 19·9%), m.p. 135·5°.

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