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Synthesis of 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoic acid [3,3,4,4-tetrafluorochlorambucil]

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Abstract

Reaction of 2,2-dichloro-2-(4′-nitrophenyl)acetonitrile with mercury(II) oxide/pyridinium poly(hydrogen fluoride), (aqueous work-up), gave 2,2-difluoro-2-(4′-nitrophenyl)acetamide, from which were made the parent acid and thence its acid chloride. This and ethyl propanedioate/methyl lithium afforded ethyl 4,4-difluoro-4-(4′-nitrophenyl)-3-oxobutanoate, converted by SF_4/HF into ethyl 3,3,4,4-tetrafluoro-4-(4′-nitrophenyl)butanoate. Catalytic hydrogenation of the nitro-group then gave the 4′-amine, which was bis(hydroxyethylated) using oxirane. Conversion to the bis(chloroethyl) analogue utilized Ph_3P/CCl_4, whence acidic hydrolysis afforded 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoic acid.

Keywords: 4-[4′-Bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoic acid; 3,3,4,4-Tetrafluorochlorambucil synthesis

1. Introduction

In previous papers, we have described fluorinated derivatives of the anti-cancer drug chlorambucil [1], which have 3,3-difluoro- [2] and 3-trifluoromethyl-substituents [3]. A *meta*-isomer of chlorambucil, carrying fluorine in the 4,4-positions, was also made, but not 4,4-difluorochlorambucil itself, since the required amino intermediate rapidly lost its fluorine by hydrolysis [4]. The reactivities of 3- and 4-aminobenzotrifluoride [5] show that a trifluoromethyl side-chain on an arene ring is destabilized much more by a *para*-amino-group than by a *meta*. However, it was also considered relevant that, whereas 1,1-difluoro-1,1-diphenylmethane is very susceptible to hydrolysis [6], 1,1,2,2-tetrafluoro-1,2-diphenylethane is quite stable [7]. Thus, it appeared that 3,3,4,4-tetrafluorochlorambucil should be sufficiently stable to justify its synthesis.

2. Results and discussion

The preparative sequence began from 4-nitrophenylacetonitrile, which was chlorinated under radical conditions (Cl_2/UV radiation) to give 2,2-dichloro-2-(4′-nitrophenyl)acetonitrile (**1**) [8]. Mercury(II) oxide/pyridinium poly(hydrogen fluoride) [9] exchanged fluorine for chlorine efficiently, but the supposed primary product was hydrolysed, presumably during the aqueous work-up, affording 2,2-difluoro-2-(4′-nitrophenyl)acetamide (**2**). Hydrolysis to the free acid (**3**) was best achieved using a mixture of concentrated hydrochloric acid and refluxing ether. Reaction with phosphorus pentachloride then gave the very moisture-sensitive 2,2-difluoro-2-(4′-nitrophenyl)acetyl chloride (**4**).

A standard nucleophilic attack on the >C=O function of (**4**) by the lithio-derivative of ethyl propanedioate [made from $EtO_2CCH_2CO_2H$ and MeLi] was then carried out. The major product was ethyl 4,4-difluoro-4-(4′-nitrophenyl)-3-oxobutanoate (**5**), about 65% of which existed in the enol form (the enol form of $CF_3COCH_2CO_2Et$ predominates [10,11]). Though purification presented no difficulty, (**5**) was accompanied by two minor by-products, which were not fully characterized, but very probably were methyl 2,2-difluoro-2-(4′-nitrophenyl)acetate (**6**), and 1,1-difluoro-1-(4′-nitrophenyl)propan-2-one (**7**). These almost certainly arose from reactions of (**4**) with lithium methoxide and lithium methyl, respectively, both very likely to be present in the system.

The reaction of crude (**5**) with sulfur tetrafluoride/hydrogen fluoride at room temperature gave ethyl 3,3,4,4-tetrafluoro-4-(4′-nitrophenyl)butanoate (**8**) as the major

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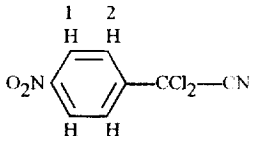
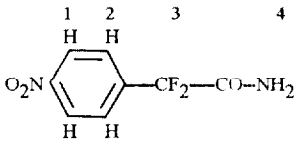
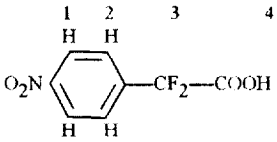
product, but the yield was only moderate (42%) and many minor by-products were also formed. Of these, some undoubtedly arose from impurities in the starting material (**5**), but it later emerged that the sample of sulfur tetrafluoride used in the reaction had also contained impurities, and it may well be that good quality material would give a better result. The major by-product present (6%) appeared to be ethyl 3,4,4-trifluoro-4-(4′-nitrophenyl)but-2-*Z*-enoate (**9**), though it was not characterized rigorously. The NMR spectrum showed appropriate peaks, including a coupling at 31 Hz, typical of trans >CH=CF<. It is possible of course that this product (**9**) was formed by direct exchange of OH for F in the enol form of (**5**). Alternatively, since the nitro-ester (**8**) began to decompose at temperatures above 110°C, giving the same butenoate (**9**), the mode of formation of the latter may well have been a reaction of this type. Trans (antiperiplanar) elimination of HF from the rotational isomer of (**8**) with least steric interactions would form the *Z*-stereoisomer.

Reduction of the nitro-group of (**8**) was first done with tin(II) chloride/hydrochloric acid, but isolation of the product was troublesome, and hydrogenation of (**8**) (palladized carbon catalyst) was preferable. The arylamine, ethyl 4-(4′-aminophenyl)-3,3,4,4-tetrafluorobutanoate (**10**) was isolated and characterized, but above about 80°C, decomposition set in. The next stage, hydroxyethylation of the aminophenyl group by use of oxirane/16 M acetic acid [2–4], was therefore carried out in the usual way, but using the amine hydrochloride (**11**). Conversion to ethyl 3,3,4,4-tetrafluoro-4-[4′-bis(2″-hydroxyethyl)aminophenyl]butanoate (**12**) occurred in 62% yield. Triphenylphosphine in carbon tetrachloride [12,13] then, as usual for this type of compound [2–4], gave an efficient conversion to ethyl 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoate (**13**).

The final stage in the synthesis, hydrolysis of the ester group, was accomplished with concentrated hydrochloric acid to give the target product, 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoic acid (**14**) as a crystalline solid. This acid gradually decomposed at temperatures above 100°C and also showed some instability towards prolonged exposure to light. Preliminary testing [K.R. Harrap, A.B. Foster, M. Jarman, personal communication] of (**14**) for alkylating activity by examining the rate of hydrolysis of the chloroethyl groups (at 37°C, pH 7.4) showed that this reaction was accompanied by more deep-seated decomposition. This was found to consume eventually three equivalents of base, and mass spectrometry indicated the probable formation of the function –C(=O)–CF=CH– [K.R. Harrap, A.B. Foster, M. Jarman, personal communication]. Biological testing was not carried out, therefore. It appears that the presence of fluorine at position 3 of compounds of the type of (**14**) does reduce the effects of activation by *para*-amino groups on fluorine at position 4, but not sufficiently so for their use as drugs (Tables 1–5).

Table 1
Nuclear magnetic resonance data for compounds **1–3**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
				(1)
			in $CDCl_3$	
^1H NMR				
1	AA'BB'	1	8.36	$J_{1,2} = 9$
2	AA'BB'	1	8.06	
				(2)
			in d^6 acetone	
^1H NMR				
1	AA'BB'	1	8.37	$J_{1,2} = 9$
2	AA'BB'	1	7.96	
4	bs	1	7.3	
^{19}F NMR				
3	s	-	103.3	
				(3)
			in d^6 acetone	
^1H NMR				
1	AA'BB'	2	8.41	$J_{1,2} = 9$
2	AA'BB'	2	7.96	
4	bs	1	12.1	
^{19}F NMR				
3	s	-	103.7	

Structures of all the compounds made followed from their analytical data and their ^1H and ^{19}F NMR spectral characteristics. Infrared spectra did not provide conclusive structural information, but the peaks displayed were in accord with the groups present.

3. Experimental details

General procedures were as described previously [2]. Ether means diethyl ether.

*3.1. 2,2-Dichloro-2-(4′-nitrophenyl)acetonitrile (**1**)*

Chlorine was bubbled slowly during 48 h through a melt of 4-nitrophenylacetonitrile (60 g) at 122°C, which was being irradiated by UV light (low-pressure lamp). Distillation in vacuo gave (i) a pale yellow liquid, (**1**) (70 g), b.p. 112°C/0.1 mm Hg (the cited [8] b.p. was 149–149.5°C, but presumably the pressure was omitted); and (ii) starting material (5 g). Effective chlorination only proceeded between

Table 2
Nuclear magnetic resonance data for compounds **4** and **5**

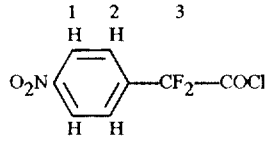
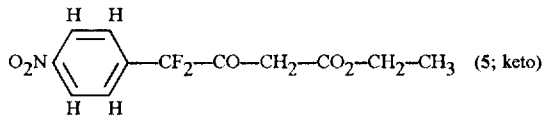
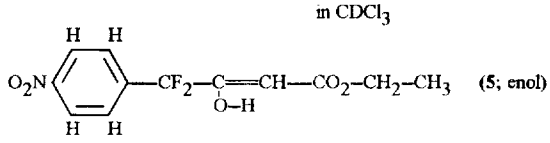
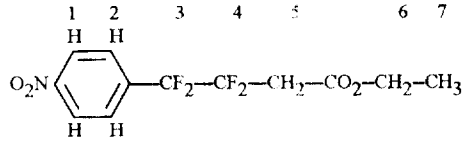
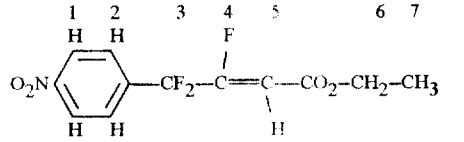
Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
	1 2 3			
				(4)
			in $CDCl_3$	
^1H NMR				
1	AA'BB'	1	8.41	$J_{1,2} = 9$
2	AA'BB'	1	7.84	
^{19}F NMR				
3	s	-	101.1	
	1 2 3 4 5 6			
				(5; keto)
			in $CDCl_3$	
				(5; enol)
	1 2 7 8 9 10 11			
^1H NMR				
1	AA'BB'	2	8.30	$J_{1,2} = 9$
2	AA'BB'	2	7.78	
4	s	0.71	3.78	
5,10	q	2	4.20/4.27	$J_{5,6} = 7$
6,11	t	3	1.25/1.32	
8	bs	0.65	12.0	
9	s	0.65	5.69	
^{19}F NMR				
3	s	0.7	104.8	
7	s	1.3	105.1	

Table 3
Nuclear magnetic resonance data for compounds **8** and **9**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
	1 2 3 4 5 6 7			
				(8)
			in $CDCl_3$	
^1H NMR				
1	AA'BB'	2	8.32	$J_{1,2} = 9$
2	AA'BB'	2	7.78	
5	tt	2	3.18	$J_{4,5} = 17$
6	q	2	4.23	$J_{6,7} = 7$
7	t	3	1.30	
^{19}F NMR				
3	tt	1	112.1	$J_{3,4} = 7$; $J_{3,5} = 2$
4	ctt	1	111.6	
	1 2 3 4 5 6 7			
				(9)
			in $CDCl_3$	
^1H NMR				
1	AA'BB'	2	8.40	$J_{1,2} = 9$
2	AA'BB'	2	7.85	
5	d	1	6.00	$J_{4,5} = 31$
6	q	2	4.27	$J_{6,7} = 7$
7	t	3	1.31	
^{19}F NMR				
3	d	2	103.5	$J_{3,4} = 15$
4	dt	1	107.4	

120 and 130°C, and even so was not very reproducible. Reaction sometimes ceased altogether, though it could usually be restarted after the melt had been distilled.

Chlorination using sulfur dichloride dioxide at 130°C for 24 h in a sealed tube was successful, but could not be scaled up to a practicable level.

3.2. 2,2-Difluoro-2-(4'-nitrophenyl)acetamide (2)

Product (**1**) (28.4 g) was added slowly, during 2 h, to a stirred suspension of yellow mercury(II) oxide (27.2 g) in pyridinium poly(hydrogen fluoride) (150 ml) kept at 20°C. The colour of the mixture changed from orange to white. After being stirred for a further 1 h at 20°C and 1 h at 55°C, the mixture was cooled and poured carefully into ice/water (300 g). The precipitate was filtered off, dried and extracted with two portions of refluxing chloroform and the extracts were concentrated to leave a white solid (22.0 g). The aqueous filtrate was continuously extracted with chloroform for 5 h and the extract dried and concentrated to give further solid (8.7 g). Recrystallization of the combined solids from chloroform gave white needles of (**2**) (19.7 g) m.p. 128–129.5°C (Found: C, 44.4; H, 3.0; F, 17.4; N, 12.9. $C_8H_6F_2N_2O_3$ requires C, 44.4; H, 2.8; F, 17.6; N, 13.0%).

Variations of reaction temperature from 0 to 55°C and of the final stage time from 1 to 24 h, and lower proportions of the fluorinating system, had little effect on the yield.

3.3. 2,2-Difluoro-2-(4'-nitrophenyl)acetic acid (3)

Amide (**2**) (19.7 g) was stirred with a refluxing mixture of ether (250 ml) and concentrated hydrochloric acid (250 ml) for 48 h. Water (200 ml) was added to the cooled mixture, the organic layer separated and the aqueous layer extracted with ether. The combined ether layers were extracted with saturated aqueous sodium bicarbonate (2 × 50 ml). The aqueous extracts were acidified (conc. HCl) and re-extracted with ether, and these ether extracts were dried and concentrated. Recrystallization from benzene afforded white needles of acid (**3**) (15.0 g) m.p. 187–189.5°C (Found: C, 44.8; H, 2.5; F, 17.5; N, 6.2. $C_8H_5F_2NO_4$ requires C, 44.3; H, 2.3; F, 17.5; N, 6.4%).

3.4. 2,2-Difluoro-2-(4'-nitrophenyl)acetyl chloride (4)

Acid (**3**) (15.0 g) and phosphorus pentachloride (14.4 g) were mixed and heated at 100°C for 10 min. The phosphorus

Table 4
Nuclear magnetic resonance data for compounds **10** and **12**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 2 3 4 5 6 7 8				
H_2N–C$_6$H$_4$–CF_2–CF_2–CH_2–CO_2–CH_2–CH_3 **(10)**				
		in CCl_4		
^{1}H NMR				
1	s	2	3.84	
2	AA'BB'	2	6.57	$J_{2,3} = 9$
3	AA'BB'	2	7.24	
6	tt	2	2.97	$J_{5,6} = 17$
7	q	2	4.14	$J_{7,8} = 7$
8	t	3	1.25	
^{19}F NMR				
4	tt	1	111.3	$J_{4,5} = 7$; $J_{4,6} = 2$
5	ctt	1	113.1	
1 2 3 4 5 6 7 8 9 10				
(HO-CH_2-CH_2)$_2$N–C$_6$H$_4$–CF_2–CF_2–CH_2–CO_2–CH_2–CH_3 **(12)**				
		in $CDCl_3$		
^{1}H NMR				
1	bs	2	4.56	
2	cm	4	C3.75	
3	cm	4	C3.52	
4	AA'BB'	2	6.68	$J_{4,5} = 9$
5	AA'BB'	2	7.37	
8	t	2	3.09	$J_{7,8} = 17$
9	q	2	4.18	$J_{9,10} = 7$
10	t	3	1.25	
^{19}F NMR				
6	t	1	110.8	$J_{6,7} = 7$
7	tt	1	113.0	

Table 5
Nuclear magnetic resonance data for compounds **13** and **14**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 2 3 4 5 6 7 8 9				
(Cl-CH_2-CH_2)$_2$N–C$_6$H$_4$–CF_2–CF_2–CH_2–CO_2–CH_2–CH_3 **(13)**				
		in $CDCl_3$		
^{1}H NMR				
1,2	cm	8	C3.68	
3	AA'BB'	2	6.71	$J_{3,4} = 9$
4	AA'BB'	2	7.44	
7	tt	2	3.08	$J_{6,7} = 17$
8	q	2	4.19	$J_{8,9} = 7$
9	t	3	1.25	
^{19}F NMR				
5	tt	1	110.9	$J_{5,6} = 7$; $J_{5,7} = 2$
6	tt	1	112.8	
1 2 3 4 5 6 7 8				
(Cl-CH_2-CH_2)$_2$N–C$_6$H$_4$–CF_2–CF_2–CH_2–CO_2–H **(14)**				
		in $CDCl_3$		
^{1}H NMR				
1,2	cm	8	C3.69	
3	AA'BB'	2	6.71	$J_{3,4} = 9$
4	AA'BB'	2	7.42	
7	tt	2	3.15	$J_{6,7} = 17$
8	bs	1	11.1	
^{19}F NMR				
5	tt	1	110.8	$J_{5,6} = 7$; $J_{5,7} = 2$
6	ctt	1	113.0	

oxychloride formed was distilled off in vacuo, to leave (**4**), as a pale yellow liquid (16.1 g), b.p. 60–65°C/15 mm Hg. Being very moisture-sensitive, this was used immediately, without further purification.

3.5. Ethyl 4,4-difluoro-4-(4′-nitrophenyl)-3-oxobutanoate (5)

Methyl lithium in hexane (200 ml; 1.2 M) was added slowly, with stirring, to a solution of ethyl propanedioate (16.3 g; dried over molecular sieves) and 2,2′-bipyridyl (30 mg) in dry tetrahydrofuran (274 ml) cooled at −70°C. By removing the cooling bath, the temperature was allowed to rise slowly to −5°C and, when a pink colour persisted, the mixture was recooled to −70°C. Acid chloride (**4**) (16.1 g), in dry tetrahydrofuran (50 ml) was added carefully; a red colour developed and the temperature rose to −55°C, but, over 10 min, fell again to −70°C. The mixture was then poured carefully into a stirred mixture of ether (600 ml) and hydrochloric acid (300 ml; 1 M). The organic layer was separated, washed with aqueous $NaHCO_3$, then water, dried and concentrated to a red liquid (16.8 g).

Part (5.0 g) was separated by column chromatography (column 51×2.5 cm; solvent, benzene) to give: (i) (0.03 g) R_f 0.83; (ii) (0.33 g) R_f 0.29; (iii) (4.2 g) R_f 0.17. Fraction (i) had an IR peak at 1770 cm^{-1}, and was probably methyl 2,2-difluoro-2-(4′-nitrophenyl)acetate (**6**). Fraction (ii) had an IR peak at 1760 cm^{-1}, and was probably 1,1-difluoro-1-(4′-nitrophenyl)propan-2-one (**7**). Both showed typical NMR peaks for the aryl and the CH_3 hydrogens and for the $>CF_2$ fluorines.

Fraction (iii) had two components; but, when recrystallized from light petroleum, the minor one (unidentified) remained as an insoluble residue, to give keto-ester (**5**) (3.8 g) m.p. 47–48°C (Found: C, 50.1; H, 3.6; F, 13.5; N, 4.8. $C_{12}H_{11}F_2NO_5$ requires C, 50.2; H, 3.9; F, 13.2; N, 4.9%).

3.6. Fluorination of ethyl 4,4-difluoro-4-(4′-nitrophenyl)-3-oxobutanoate (5)

Sulfur tetrafluoride (21 ml; later found to be impure) was slowly distilled into an autoclave (70 ml capacity) at −78°C, containing crude keto-ester (**5**) (26.0 g) and hydrogen fluoride (21 ml). The autoclave was sealed and shaken at room temperature for 16 h. It was then cooled to −78°C and the contents poured carefully into a plastic beaker; volatile materials were allowed to evaporate. Cold water (300 ml) was

added slowly and carefully, and the product extracted into ether. The extracts were washed with water, then with saturated aqueous $NaHCO_3$, dried and concentrated to leave a red liquid (25.0 g). This was distilled in vacuo through a short Vigreux column to give: (i) (3.6 g) b.p. 40–95°C; (ii) (1.2 g) b.p. 95–110°C; (iii) (15.7 g) b.p. 110–112°C. Fraction (i) was a multicomponent mixture. Fractions (ii) and (iii) were combined, and at low temperatures, crystallization occurred. The solid was purified by low temperature crystallization to give ethyl 3,3,4,4-tetrafluoro-4-(4′-nitrophenyl)butanoate (**8**), (11.7 g) m.p. 45–46°C, b.p. 112°C/0.05 mm Hg, R_f 0.5 (benzene) (Found: C, 46.7; H, 3.3; F, 24.3; N, 4.2. $C_{12}H_{11}F_4NO_4$ requires C, 46.6; H, 3.6; F, 24.6; N, 4.5%). The liquid residue from (ii) and (iii) was subjected to column chromatography (column, 51 × 2.4 cm; solvent, benzene), affording (iv) (1.8 g) R_f 0.8, two unidentified components; and (v) (1.7 g) R_f 0.58. Fraction (v) was not completely characterized, but was probably ethyl 3,4,4-trifluoro-4-(4′-nitrophenyl)but-2-*Z*-enoate [9].

*3.7. Ethyl 4-(4′aminophenyl)-3,3,4,4-tetrafluorobutanoate (**10**)*

(A) Tin(II) chloride hydrate (0.94 g) was added in portions during 30 min to a stirred suspension of compound (**8**) (0.35 g) in ethanol (0.5 ml) and concentrated hydrochloric acid (0.7 ml) at 50°C. After 15 min at 60°C, the system was cooled and then poured into aqueous NaOH containing ice. After extraction with ether the extracts were dried, and dry HCl gas passed through, to give a precipitate. Recrystallization from carbon tetrachloride afforded the hydrochloride (**11**) [(0.17 g), m.p. 170°C (dec)] of amine (**10**).

(B) A solution of (**8**) (2.0 g) in ethanol (70 ml) and ethanolic hydrogen chloride (3 ml; 9 M) containing palladized carbon (10%; 0.25 g) was shaken in an atmosphere of hydrogen at 10°C and normal pressure. When the correct volume of hydrogen had been consumed, the solution was filtered and concentrated in vacuo. Ether was added and the solution was then washed with hydrochloric acid (10 ml; 0.5 M), little amine being extracted. The ether layer (containing the product) was washed with saturated aqueous $NaHCO_3$ (3 ml), dried and concentrated to leave amine (**10**) (1.5 g). Purification by column chromatography (column 30 × 2.4 cm; solvent, chloroform) gave a liquid which solidified at −20°C. It was ethyl 4-(4′-aminophenyl)-3,3,4,4-tetrafluorobutanoate (**10**), m.p. 31°C (Found: C, 51.6; H, 4.8; F, 26.8; N, 5.3. $C_{12}H_{13}F_4NO_2$ requires C, 51.6; H, 4.7; F, 27.2; N, 5.0%).

*3.8. Ethyl 3,3,4,4-tetrafluoro-4-[4′-bis(2″-hydroxyethyl)aminophenyl]butanoate (**12**)*

Oxirane (2.7 ml) was added to a solution of salt (**11**) (5.35 g) in acetic acid (25 ml, 16 M) at 0°C. After being allowed to attain room temperature, the solution was stirred for 72 h. It was then concentrated, poured into saturated aqueous $NaHCO_3$ and the solution extracted with ether. The extracts were washed, dried and concentrated to leave an oil (6.9 g). A portion (0.4 g) was separated by column chromatography (column 35 × 2.4 cm; solvent, chloroform:ether, 1:1) to give three fractions: (i) (0.01 g) R_f 0.45; (ii) (0.05 g) R_f 0.35; (iii) (0.25 g) R_f 0.24. Fractions (i) and (ii) were not identified, while (iii) was ethyl 3,3,4,4-tetrafluoro-4-[4′-bis(2″-hydroxyethyl)aminophenyl]butanoate (**12**), a clear liquid (Found: C, 52.3; H, 5.8; F, 20.4; N, 3.9. $C_{16}H_{21}F_4NO_4$ requires C, 52.3; H, 5.8; F, 20.7; N, 3.8%).

*3.9. Ethyl 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoate (**13**)*

A stirred solution of triphenylphosphine (10.8 g) in dry carbon tetrachloride (20 ml) was added to the oil described in Section 3.8 (6.1 g) in an atmosphere of dry nitrogen. After 3.5 h of refluxing, a light brown precipitate had formed; it was filtered off and washed with ether. The combined liquids were concentrated, and the solid residue extracted with refluxing ether. The combined filtered extracts were concentrated to half volume, refluxed, recooled and filtered again. The solution was concentrated to leave an oil, which was subjected to column chromatography (column 60 × 2.4 cm; solvent, benzene) to give four fractions. Three of these were not identified: (i) two components, (0.02 g) R_f 0.69, R_f 0.58; (iii) (0.4 g) R_f 0.32; and (iv) (0.3 g) R_f 0.11–0.10. Fraction (ii), (3.06 g) R_f 0.5, which solidified on standing and was recrystallized from light petroleum (b.p. 40–60°C), was compound (**13**), long needles m.p. 47°C (Found: C, 48.0; H, 4.7; Cl, 17.6; F, 19.1; N, 3.4. $C_{14}H_{19}Cl_2F_4NO_2$ requires C, 47.5; H, 4.7; Cl, 17.5; F, 18.8; N, 3.5%).

*3.10. 4-[4′-bis(2″-chloroethyl)aminophenyl]-3,3,4,4-tetrafluorobutanoic acid (**14**)*

Ester (**13**) (2.2 g) was stirred at 65°C for 1.5 h with concentrated hydrochloric acid (18 ml). The solution was cooled, poured into water, extracted with ether, and the extracts washed, dried and concentrated in vacuo (< 50°C). The liquid residue solidified and was recrystallized from light petroleum (b.p. 40–60°C)/carbon tetrachloride to give acid (**14**) as plates (1.55 g), m.p. 102–103°C (decomp.) (Found: C, 45.1; H, 3.6; Cl, 18.8; F, 20.0; N, 3.0. $C_{14}H_{15}Cl_2F_4NO_2$ requires C, 44.7; H, 4.0; Cl, 18.8; F, 20.2; N, 3.7%).

3.11. NMR spectroscopy

Nuclear magnetic resonance spectra were measured using a Perkin Elmer R12B machine: ^1H chemical shifts (60 MHz) are quoted on the δ scale in parts per million downfield of tetramethylsilane, and ^{19}F (56.4 MHz) in ppm upfield of trichlorofluoromethane, both internal standards. The solvent used is stated for each compound.

Signals are designated by: s (singlet), d (doublet), t (triplet), q (quartet), AA′BB′, m (incompletely resolved multi-

plet), b (broad), c (complex), col. (collapsed, with most of the intensity in the central peaks). Where a chemical shift value is preceded by C, this indicates the center of an involved multiplet.

When a coupling is recorded for a peak, the corresponding coupling was present also in the other designated peak.

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