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Synthesis of 4-[3′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoic acid [4,4-difluoro-*meta*-chlorambucil]

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Abstract

The synthetic sequence to make 4-[4′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoic acid {4,4-difluorochlorambucil} was not taken beyond the intermediate stage involving methyl 4,4-difluoro-4-(4′-aminophenyl)butanoate, since this amine was hydrolytically unstable. Reaction of methyl 4-(3′-nitrophenyl)-4-oxobutanoate with sulfur tetrafluoride, followed by hydrogenation, afforded the stable isomer, methyl 4,4-difluoro-4-(3′-aminophenyl)butanoate. Bis(hydroxyethylation) by treatment with oxirane, conversion of OH to Cl by Ph_3P/CCl_4, and then hydrolysis of the ester group, gave 4-[3′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoic acid {4,4-difluoro-*meta*-chlorambucil}. © 1997 Elsevier Science S.A.

Keywords: 4-[3′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoic acid; 4,4-Difluoro-*meta*-chlorambucil synthesis

1. Introduction

The drug chlorambucil [1] is important in cancer chemotherapy, and a brief account of the way by which its degradative metabolic pathway might be modified in fluorinated analogues has been given in our earlier papers, describing derivatives carrying 3,3-difluoro- [2] and 3-trifluoromethyl-substituents [3]. The present work was aimed at the synthesis of chlorambucil analogues having 4,4-difluoro-substituents. It was recognized that when the fluorine in these was adjacent to a benzene ring bearing a substituted *para*-amino-group, it might well show some instability. This applies for most trifluoromethyl side chains that are carried on arene or heteroarene rings with amino-groups in *para*-positions, an effect first demonstrated for 4-aminobenzotrifluoride [4]. However, such compounds can usually be isolated, and there seemed a reasonable chance that fluorines α to the benzene ring in chlorambucil analogues would not be particularly unstable.

2. Results and discussion

Syntheses of 4,4-difluorochlorambucil were attempted, starting from methyl 4-(4′-aminophenyl)-4-oxobutanoate (**1**) [5,6]. Direct reaction with diethylaminosulfur trifluoride (DAST) failed: if any product was formed, it regenerated the ketone (**1**) during the work-up. The *N*-acetyl-, *N*-bis(hydroxyethyl)-, and *N*-bis(chloroethyl)-derivatives of (**1**) also gave no fluorinated products from reactions with DAST or with sulfur tetrafluoride.

Accordingly, the corresponding 4′-nitro-compound (**2**) was made by oxidation of (**1**) with trifluoroacetic anhydride/hydrogen peroxide [7]. Reaction at the amino group predominated, and there was little attack on the ketone function. Fluorination of (**2**) by DAST proceeded very slowly, but reaction with sulfur tetrafluoride/hydrogen fluoride at room temperature afforded two products: (a) the desired methyl 4,4-difluoro-4-(4′-nitrophenyl)butanoate (**3**) (58%), and (b) 1-(1′,1′,4′,4′,4′-pentafluorobutyl)-4-nitrobenzene (**4**) (24%). In general, exchange of F for O by SF_4 occurs more readily with keto functions than with carboxy functions; the reaction time may have been longer than was necessary, and excess SF_4 used, but ester groups are not usually converted into CF_3 at temperatures as low as this [8].

Reduction of the nitro-difluoro-ester (**3**) using hydrogen and a palladium catalyst in a solvent of methanol containing acetic acid (not especially dried) consumed more hydrogen than was required to convert NO_2 to NH_2. The sole product isolated was methyl 4-(4′-aminophenyl)butanoate (**5**). Presumably, following formation of the amino group, the difluoromethylene moiety was hydrolysed to a carbonyl (i.e.

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regenerating starting material (**1**)). This group, being adjacent to the arene ring, was then reduced to methylene, to give the product obtained (**5**). Hydrogenation was then carried out over a platinum catalyst in ethanolic hydrogen chloride. The hydrochloride of methyl 4-(4′-aminophenyl)-4,4-difluorobutanoate (**6**) was obtained, but, when water was added, it reverted rapidly to the original ketone (**1**).

Thus, it appeared unlikely that tertiary amines derived from the free base of **6** would show sufficient stability to be of practical use and so this synthetic sequence was not pursued further. Though 4-aminobenzotrifluoride is not very stable, it does not lose fluorine during normal handling or conversion into fused-ring heterocycles [9,10]. However, the behaviour of amine **6** resembled that of 1-(1′,1′-difluoroethyl)-4-nitrobenzene [11].

Derivatives based on *m*-aminobenzotrifluoride do not normally show hydrolytic instability. The synthesis of an isomer of 4,4-difluorochlorambucil carrying the tertiary amine side chain in the *meta*-position was therefore undertaken. The starting point was 4-oxo-4-phenylbutanoic acid [12], which was nitrated in the *m*-position [13,14] (small proportions of the other isomers were readily removed by recrystallization) and esterified to give methyl 4-(3′nitrophenyl)-4-oxobutanoate (**7**) [13]. This was treated with SF_4/HF at room temperature and with a short reaction time. The major product was methyl 4,4-difluoro-4-(3′-nitrophenyl)butanoate (**8**) (64%), with very little 1-(1′,1′,4′,4′,4′-pentafluorobutyl)-3-nitrobenzene (**9**) (1.5%). Hydrogenation of the nitro-ester (**8**) (palladized carbon catalyst) yielded the amine, methyl 4-(3′aminophenyl)-4,4-difluorobutanoate (**10**), which, as expected, and unlike **6**, was relatively stable, though it was purified via the hydrochloride, since some decomposition occurred on distillation.

In the original work [1], the aminophenyl group in this type of compound was hydroxyethylated by oxirane in dilute acetic acid. Our synthesis of 3,3-difluorochlorambucil [2] utilized 16 M acid, and a similar reaction for 72 h at room temperature, converted (**10**) to methyl 4,4-difluoro-4-[3′-bis(2″-hydroxyethyl)aminophenyl]butanoate (**11**). A small amount of the analogous mono-hydroxyethyl secondary amine was also present. Conversion of OH to Cl was carried out using triphenylphosphine in carbon tetrachloride [15], and, as in the earlier case [2], the target 3′-bis(2″-chloroethyl)-derivative (**12**) was accompanied by a second product, methyl 4,4-difluoro-4-[3′-(4″-morpholinyl)-phenyl]butanoate (**13**). The formation of **13** is understandable, via intermediates corresponding to steps in the pathways proposed for this reaction [16,17].

The final stage in the synthesis, hydrolysis of the ester group, was carried out using concentrated hydrochloric acid to give the product sought, 4-[4′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoic acid (**14**) as a crystalline solid. Preliminary biological tests on this acid (**14**) [18] did not show a therapeutic index as good as that of chlorambucil.

The structures of all the compounds reported (**1–14**) were confirmed by their elemental analyses, and particularly their ^{1}H- and ^{19}F-NMR spectral data. Infrared spectra provided further information, the peaks displayed being in accord with the groups present.

3. Experimental details

General procedures and techniques were carried out as described previously [2]. Ether means diethyl ether.

3.1. Methyl 4-(4′-aminophenyl)-4-oxobutanoate (1)

Acetanilide and succinic anhydride in the presence of aluminium chloride [5] afforded 4-[4′-(acetylamino)phenyl]-4-oxobutanoic acid. It was found advantageous to carry out the reaction in 1,2-dichloroethane as solvent. The product (yield 70%) had m.p. 204–206 °C (cited [5], 202–205 °C). Esterification with refluxing methanol/H_2SO_4 [6] also removed the *N*-acetyl group, as, surprisingly, did the reaction of the acid with a medium of acetyl chloride and methanol. The product, in both cases, was **1**, m.p. 167 °C (cited [6], 164–167 °C).

3.2. Methyl 4-(4′-nitrophenyl)-4-oxobutanoate (2)

Trifluoroacetic anhydride (33.6 g) was added slowly to a vigorously-stirred suspension of hydrogen peroxide (4.05 ml; 90%) in dichloromethane (70 ml) at 0°. After 10 min, the cooling bath was removed, and amine **1** (10.3 g) in dichloromethane (150 ml) was added slowly. The mixture was refluxed for 15 min, cooled, washed three times with water then with saturated aq. $NaHCO_3$, dried and concentrated to leave a red solid. This was recrystallized from light petroleum (b.p. 40–60 °C) to give **2** (7.35 g) as colourless needles, m.p. 62–64 °C (Found: C, 55.6; H, 4.5; N, 5.8. $C_{11}H_{11}NO_5$ requires C, 55.7; H, 4.7; N, 5.9%).

3.3. Methyl 4,4-difluoro-4-(4′-nitrophenyl)butanoate (3)

Sulfur tetrafluoride (24 ml) was slowly distilled into an autoclave (70 ml capacity) at −78 °C containing (**2**) (4.4 g) and hydrogen fluoride (15 ml). The autoclave was sealed and shaken at room temperature for 28 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 aq $NaHCO_3$, dried and concentrated to leave a red solid (4.6 g). Column chromatography (column, 38 cm×2.4 cm; solvent, benzene: ether, 9:1) afforded two products: (i) Rf 0.8; (ii) Rf 0.58. Distillation in vacuo of fraction (i) gave 1-(1′,1′,4′,4′,4′-pentafluorobutyl)-4-nitrobenzene (**4**) (1.2 g), b.p. 108 °C/0.9 mm Hg (Found: C, 44.8; H, 3.0; F, 35.4; N, 5.1. $C_{10}H_8F_5NO_2$ requires

C, 44.6; H, 3.0; F, 35.3; N, 5.2%). Low temperature recrystallization of fraction (ii) from carbon tetrachloride/light petroleum (b.p. 40–60 °C) afforded methyl 4,4-difluoro-4-(4′-nitrophenyl)butanoate (**3**) (2.8 g), m.p. 55 °C (Found: C, 51.1; H, 4.3; F, 14.9; N, 5.3. $C_{11}H_{11}F_2NO_4$ requires C, 51.0; H, 4.3; F, 14.7; N, 5.4%).

3.4. Catalytic hydrogenation of methyl 4,4-difluoro-4-(4′-nitrophenyl)butanoate (3)

(A) Compound (**3**) (0.45 g), methanol (20 ml), acetic acid (5 ml) and palladized carbon (10%; 50 mg) were shaken together in an atmosphere of hydrogen at 20 °C and normal pressure until take-up ceased (more than the expected volume having been absorbed). The solution was filtered and concentrated, then washed with saturated aq. $NaHCO_3$, and the amine product extracted with chloroform. Washing, drying and evaporation of solvent, followed by recrystallization from light petroleum, left methyl 4-(4′-aminophenyl)butanoate (**5**) (0.26 g), m.p. 42 °C (cited [1], 42 °C).

(B) Compound (**3**) (1.0 g), ethanol (40 ml), platinum (IV) oxide (100 mg) and ethanolic hydrogen chloride (15 ml; 9 M) were shaken together in a Burgess–Parr apparatus under 4 atm. pressure of hydrogen at 20 °C. When the correct volume for reduction of the NO_2 group had been taken up, reaction ceased, and the solution was filtered, dried and concentrated. The solid product was washed with dry tetrahydrofuran and dried in vacuo, to give methyl 4-(4′-aminophenyl)-4,4-difluorobutanoate hydrochloride (**6**) (0.8 g).

When **6** (0.5 g) was left in water (10 ml) for 1 h, followed by extraction with chloroform, drying and concentration, in the usual way, methyl 4-(4′-aminophenyl)-4-oxobutanoate (**1**) (0.3 g) was the only product to be isolated.

3.5. Methyl 4-(3′-nitrophenyl)-4-oxobutanoate (7)

4-Oxo-4-phenylbutanoic acid [12] was nitrated as described in Ref. [13], at −5 °C. After removal of the minor isomers by recrystallization from water/ethanol, 4-(3′nitrophenyl)-4-oxobutanoic acid (68%) was obtained, m.p. 167 °C (cited [13], 162–164 °C; [14], 165–166 °C). This (20 g) was esterified with acetyl chloride (6.6 ml) and methanol (70 ml). The product, isolated as usual and recrystallized from ethanol/water, was methyl 4-(3′-nitrophenyl)-4-oxobutanoate (**7**) (19.5 g), m.p. 69 °C (cited [13], 68–69 °C).

3.6. Methyl 4,4-difluoro-4-(3′-nitrophenyl)butanoate (8)

As in Section 3.3, ketone (**7**) (30 g), SF_4 (20 ml), and HF (15 ml) were shaken together for 2.3 h. Distillation of the product (0.25 mm Hg) gave two fractions: (i) 0.66 g, b.p. 98–116 °C; (ii) 24.5 g, b.p. 116–122 °C. Column chromatography (column, 25 cm × 2.4 cm; solvent, benzene) of fraction (i) gave 1-(1′,1′,4′,4′,4′-pentafluorobutyl)-3-nitrobenzene (**9**) (0.5 g), b.p. 106 °C/1.0 mm Hg (Found: C, 44.9; H, 3.0; F, 35.3; N, 5.2. $C_{10}H_8F_5NO_2$ requires C, 44.6; H, 3.0; F, 35.3; N, 5.2%). Low temperature recrystallization of fraction (ii) from carbon tetrachloride/light petroleum (b.p. 40–60 °C) afforded methyl 4,4-difluoro-4-(3′-nitrophenyl)butanoate (**8**) (21.0 g), m.p. 35 °C (Found: C, 51.3; H, 4.1; F, 14.4; N, 5.5. $C_{11}H_{11}F_2NO_4$ requires C, 51.0; H, 4.3; F, 14.7; N, 5.4%).

3.7. Methyl 4-(3′-aminophenyl)-4,4-difluorobutanoate (10)

Compound (**8**) (20.0 g) in ethanol (150 ml) and palladized carbon (10%; 0.3 g) were shaken together in an atmosphere of hydrogen at 5 °C and normal pressure. When the calculated volume of hydrogen had been consumed, the solution was filtered and concentrated. Water was added and the product extracted into ether, which was washed, dried and concentrated. The yellow liquid residue was dissolved in dry ether and dry hydrogen chloride passed through. The colourless precipitate of methyl 4-(3′-aminophenyl)-4,4-difluorobutanoate hydrochloride (18.6 g) had m.p. 163 °C (decomp. 170–179 °C). It was dissolved in saturated aq. $NaHCO_3$ and the solution extracted with ether. The extracts were washed, dried and concentrated to leave methyl 4-(3′-aminophenyl)-4,4-difluorobutanoate (**10**) (17.0 g) b.p. 198 °C (decomp.) (Found: C, 57.5; H, 5.7; F, 16.2; N, 6.3. $C_{11}H_{13}F_2NO_2$ requires C, 57.6; H, 5.7; F, 16.6; N, 6.1%).

3.8. Methyl 4,4-difluoro-4-[3′-bis(2″-hydroxyethyl)aminophenyl]butanoate (11)

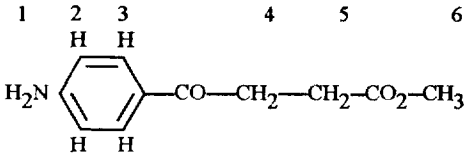
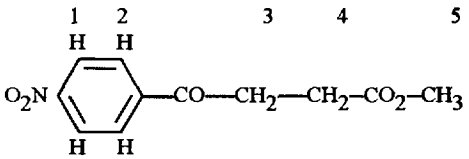
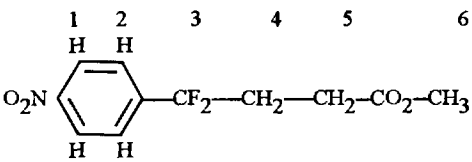
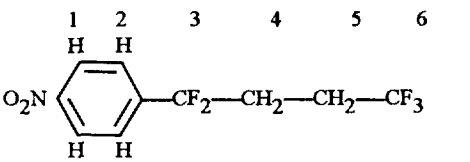
Oxirane (15.6 ml), was added to a solution of compound **10** (23.0 g) in acetic acid (125 ml, 16 M) at 0 °C. After being allowed to attain room temperature, the solution was stirred for 72 h. It was then concentrated, poured into saturated aq. $NaHCO_3$ and the solution extracted with chloroform. The extracts were washed, dried and concentrated to leave an oil (32.1 g). A portion (0.6 g) was separated by column chromatography (column 25 cm × 2 cm; solvent ether) to give three fractions: (i) (< 0.01 g), (ii) (0.05 g) and (iii) (0.47 g). Fraction (i) was not identified, whilst (ii) was characterized tentatively as the mono(2″-hydroxyethyl) analogue of **11**; (iii) was methyl 4, 4-difluoro-4-[3′-bis(2″-hydroxyethyl)aminophenyl]butanoate (**11**), a liquid which solidified, m.p. 49–50 °C (Found: C, 56.6; H, 6.7; F, 11.5; N, 4.7. $C_{15}H_{21}F_2NO_4$ requires C, 56.8; H, 6.7; F, 12.0; N, 4.4%).

The oily crude product was used for the next stage without further purification.

3.9. Methyl 4-[3′-bis(2″-chloroethyl)aminophenyl]-4,4-difluorobutanoate (12)

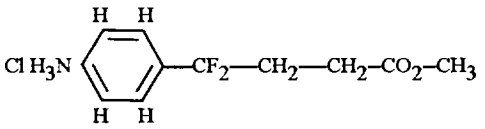
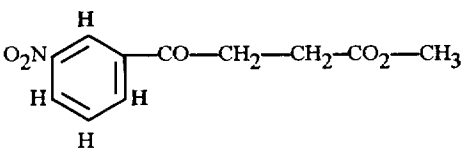
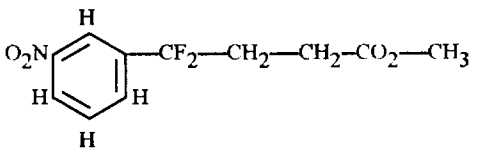
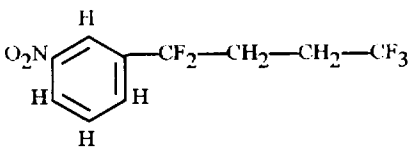
The oil described in Section 3.8 (35.0 g) in warm dry carbon tetrachloride (100 ml) was added to a stirred solution of triphenylphosphine (60.0 g) in dry carbon tetrachloride

Table 1
Nuclear magnetic resonance data for compounds **1–14**

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
 **(1)**				
in d^6 D.M.S.O.				
^{1}H NMR				
1	bs	2	6.01	
2	AA′BB′	2	6.66	$J_{2,3}=9$
3	AA′BB′	2	7.76	
4	ct	2	3.14	$J_{4,5}=6$
5	ct	2	2.61	
6	s	3	3.60	
 **(2)**				
in $CDCl_3$				
^{1}H NMR				
1	AA′BB′	2	8.33	$J_{1,2}=8$
2	AA′BB′	2	8.15	
3	ct	2	3.37	$J_{3,4}=6$
4	ct	2	2.79	
5	s	3	3.71	
 **(3)**				
in CCl_4				
^{1}H NMR				
1	AA′BB′	2	8.27	$J_{1,2}=8$
2	AA′BB′	2	7.67	
4,5	col.m	4	C2.47	
6	s	3	3.62	
^{19}F NMR				
3	ctt	–	98.7	$J_{3,4}=14$; $J_{3,5}=5$
 **(4)**				
in CCl_4				
^{1}H NMR				
1	AA′BB′	2	8.26	$J_{1,2}=8$
2	AA′BB′	2	7.68	
4,5	m	4	2.1–2.8	
^{19}F NMR				
3	ct	2	98.8	$J_{3,4}=15$
6	ct	3	67.2	$J_{5,6}=10$

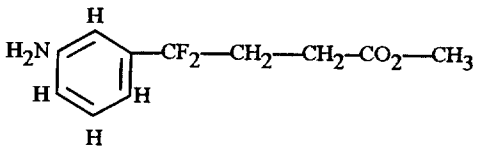
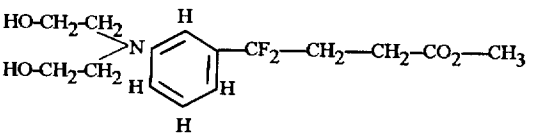
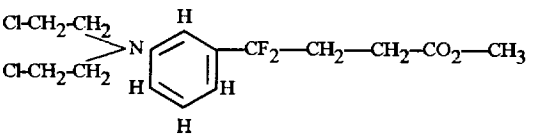
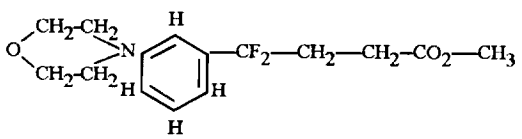
(*continued*)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 2 3 4 5 6 7				
		(6)		
in d^6 D.M.S.O.				
^{1}H NMR				
1	bs	3	4.96	
2	AA'BB'	2	7.22	$J_{2,3}=9$
3	AA'BB'	2	6.80	
5,6	col.m	4	C2.43	
7	s	3	3.57	
^{19}F NMR				
4	ct	–	91.3	$J_{4,5}=14$: $J_{4,6}=5$
1 2 3 4				
		(7)		
in d^6 acetone				
^{1}H NMR				
1	cm	4	7.7–8.8	
2	ct	2	3.46	$J_{2,3}=7$
3	ct	2	2.74	
4	s	3	3.64	
1 2 3 4 5				
		(8)		
in CCl_4				
^{1}H NMR				
1	cm	4	7.6–8.4	
3,4	col.m	4	C2.48	
5	s	3	3.59	
^{19}F NMR				
2	ctt	–	98.0	$J_{2,3}=17$: $J_{2,4}=6$
1 2 3 4 5				
		(9)		
in $CDCl_3$				
^{1}H NMR				
1	cm	1	7.5–8.5	
3,4	cm	1	1.9–2.9	
^{19}F NMR				
2	ct	2	99.2	$J_{2,3}=15$
5	ct	3	67.1	$J_{4,5}=11$

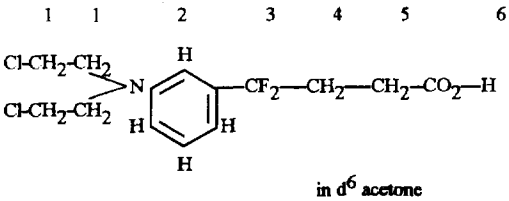
(*continued*)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 2 3 4 5 6				
 **(10)**				
in CCl_4				
^{1}H NMR				
1	bs	2	3.70	
2	cm	4	6.4–7.3	
4,5	col.m	4	C2.38	
6	s	3	3.56	
^{19}F NMR				
3	ctt	–	97.7	$J_{3,4}=16$: $J_{3,5}=6$
1 2 3 4 5 6 7 8				
 **(11)**				
in $CDCl_3$				
^{1}H NMR				
1	bs	2	4.3	
2	m	4	3.79	
3	m	4	3.54	
4	cm	4	6.4–7.4	
6,7	col.m	4	C2.47	
8	s	3	3.61	
^{19}F NMR				
5	ctt	–	97.3	$J_{5,6}=16$
1 1 2 3 4 5 6				
 **(12)**				
in CCl_4				
^{1}H NMR				
1	col.m	8	3.55	
2	cm	4	6.5–7.4	
4,5	col.m	4	C2.41	
6	s	3	3.62	
^{19}F NMR				
3	ctt	–	97.2	$J_{3,4}=16$: $J_{3,5}=6$
1 2 3 4 5 6 7				
 **(13)**				
in $CDCl_3$				
^{1}H NMR				
1	cm	4	C3.83	
2	cm	4	C3.15	
3	cm	4	6.7–7.5	
5,6	col.m	4	C2.47	
7	s	3	3.63	
^{19}F NMR				
4	ctt	–	97.4	$J_{4,5}=15$: $J_{4,6}=6$

(*continued*)

Table 1 (*continued*)

Assignments	Signals	Relative intensities	Chemical shift positions	Coupling constants
1 1 2 3 4 5 6  (14)				
in d^6 acetone				
^{1}H NMR				
1	col.m	8	3.77	
2	cm	4	6.7–7.4	
4,5	col.m	4	C2.47	
6	bs	1	9.6	
^{19}F NMR				
3	ctt	–	95.9	$J_{3,4}=15$: $J_{3,5}=6$

(100 ml) in an atmosphere of dry nitrogen. After 3 h of refluxing, a light brown precipitate, which had formed, was filtered off and washed with ether. The combined liquids were concentrated, and the 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 (36.0 g). This was subjected to column chromatography (column 80 cm×4 cm; solvent, benzene:ether, 9:1) to give three fractions: (i) Rf 0.67 (21.7 g); (ii) Rf 0.55 (1.0 g) unknown; (iii) Rf 0.48 (8.2 g).

A portion of fraction (i) was purified by short-path distillation in vacuo to give compound **12**, b.p. 160 °C/0.02 mm Hg, which solidified (Found: C, 51.0; H, 5.7; Cl, 19.9; F, 10.5; N, 3.7. $C_{15}H_{19}Cl_2F_2NO_2$ requires C, 50.9; H, 5.4; Cl, 20.0; F, 10.7; N, 4.0%).

A portion of fraction (iii) was purified by short-path distillation in vacuo to give methyl 4,4-difluoro-4-[3′-(4″-morpholinyl)phenyl]butanoate (**13**), b.p. 150 °C/0.02 mm Hg, (Found: C, 59.4; H, 6.2; F, 12.4; N, 4.7. $C_{15}H_{19}F_2NO_3$ requires C, 60.2; H, 6.4; F,12.7; N, 4.7%).

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

Ester (**12**) (5.5 g) was stirred at 85 °C for 1 h with concentrated hydrochloric acid (40 ml). The solution was poured into water, extracted with ether, and the extracts washed, dried and concentrated. Column chromatography (column 38 cm×2.4 cm; solvent, benzene:ether, 2:1) of the resultant yellow liquid (5.2 g) gave two fractions: (i) 4.86 g; (ii) 0.05 g. Fraction (i) was recrystallized from carbon tetrachloride/light petroleum (b.p. 40–60 °C) to give acid (**14**) as flat needles (3.9 g), m.p. 73.5–75 °C (Found: C, 49.7; H, 5.3; Cl, 20.8; F, 11.2; N, 4.3. $C_{14}H_{17}Cl_2F_2NO_2$ requires C, 49.4; H, 5.0; Cl, 20.8; F, 11.2; N, 4.1%).

3.11. NMR spectroscopy

Nuclear magnetic resonance spectra were measured on a Perkin–Elmer R12B machine (Table 1): ^{1}H chemical shifts (60 MHz) are quoted on the δ scale in parts per million downfield of tetramethylsilane, and ^{19}F (56.4 MHz) in p.p.m. 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 multiplet), 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 centre of an involved multiplet.

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

The complex peak patterns arising from the aryl protons of products **7–14** were as expected for the appropriate *meta*-substituted derivative. Thus, those of compound **12** (cm, 6.5–7.4) could be assigned to multiplets centred at 6.51, 6.52 and 7.15 (intensity ratio, 2:1:1), arising from H's respectively *ortho*, *para* and *meta* to the NR_2 group.

References

[1] J.L. Everett, J.J. Roberts, W.C.J. Ross, J. Chem. Soc. (1953) 2386.
[2] C.W. Buss, P.L. Coe, J.C. Tatlow, J. Fluorine Chem. 34 (1986) 83.
[3] P.L. Coe, M. Markou, J.C. Tatlow, J. Fluorine Chem. 84 (1997) 113.
[4] R.G. Jones, J. Am. Chem. Soc. 69 (1947) 2346.
[5] J.P. English, R.C. Clapp, Q.P. Cole, J. Krapcho, J. Am. Chem. Soc. 67 (1945) 2263.
[6] J.F. McEnvoy, G.R. Allen, J. Med. Chem. 17 (1974) 281.
[7] W.D. Emmons, J. Am. Chem. Soc. 76 (1954) 3468.
[8] G.A. Boswell, W.C. Ripka, R.M. Scribner, C.W. Tullock, Organic Reactions 21 (1973) 1.
[9] E. Pouterman, A. Girardet, Helv. Chim. Acta 30 (1947) 107.
[10] E.J. Forbes, M. Stacey, J.C. Tatlow, R.T. Wragg, Tetrahedron 8 (1960) 67.

[11] F. Mathey, J. Bensoam, Tetrahedron 31 (1975) 391.
[12] L.F. Somerville, C.F.H. Allen, Organic Syntheses, Coll. Vol. II, (1943) 81.
[13] E.L. Martain, J. Am. Chem. Soc. 58 (1936) 1441.
[14] C.K. Chang, Y.J. Huang, Ber. 69B (1936) 1507.
[15] J.B. Lee, J.S. Nolan, Canad. J. Chem. 44 (1966) 1331; Tetrahedron, 23 (1967) 2789.
[16] J.I.G. Cadogan, R.K. Mackie, Chem. Soc. Reviews 3 (1974) 87.
[17] I. Tömösközi, L. Gruber, L. Radics, Tetrahedron Lett. (1975) 2473.
[18] K.R. Harrap, M. Jarman, P. Workman, personal communication.