Pentafluorophenyl Esters of Dicarboxylic Acids

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Di- and half-esters of various dicarboxylic acids and dicarboxylic monoamides with pentafluorophenol were prepared. Their syntheses, properties, and spectroscopic data are reported.

Pentafluorophenylester von Dicarbonsäuren

Di- und Halbester verschiedener Dicarbonsäuren und Dicarbonsäuremonoamide mit Pentafluorophenol wurden dargestellt. Über ihre Synthesen, Eigenschaften und spektroskopischen Daten wird berichtet.

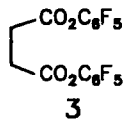
Pentafluorophenyl esters **1** were first suggested by *Kisfaludy* and coworkers for use in peptide synthesis[1]. They are readily obtainable from carboxylic acids, dicyclohexyl carbodiimide, and commercial pentafluorophenol. Since then, they have rarely been used as the active ester component in the formation of peptide bonds[2], *inter alia* in the total synthesis of the peptide antibiotic antrimycin D_v[3] and the cyclopeptide antibiotic glidobactin A[4] where they were prepared *in situ* with a protonated amine in another position of the molecule. Treatment of these salts with base liberated the amine moiety and induced formation of the desired amide bond.

Pentafluorophenyl esters generally have a reactivity towards N-nucleophiles that is comparable to acid chlorides, but they are much more stable in the presence of O-nucleophiles. This is exemplified by the fact that they may be recrystallized from ethanol and ethanol-water mixtures. We here show that they may be purified, too, by 'flash' chromatography[5] without significant drop in yield. Whereas a study of the lit.[6] suggests that they are sensitive intermediates one should avoid isolating, our results prove them to be stable under many conditions. They for instance survive contact with O- and N-nucleophiles under neutral and acidic conditions and are not attacked by thiol groups in an acidic medium (see below). These observations should stimulate their use in peptide synthesis where it is always desirable to isolate and purify intermediates and to have activated esters that are unreactive towards non-nitrogen nucleophiles[7].

In this paper we show that in the case of dicarboxylic acids, pentafluorophenyl esters are also very useful and easy to handle. We prepared di- and half-esters of dicarboxylic acids, esters of dicarboxylic monoamides, and found that an ester containing an ammonium moiety (**16**; *e.g.*) was well-characterized and stable in the solid state.

The pentafluorophenyl half-esters of dicarboxylic acids we obtained had sufficient hydrolytic stability in spite of the remaining acidic function though we observed the half-ester **9a** to be much more prone to hydrolysis or transesterification to give diacid and diester than the higher and lower homologs **8a** and **10a**.

Schemes 1 and 2 list the pentafluorophenyl esters described in this paper.



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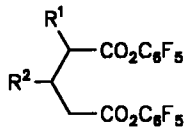
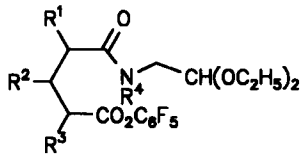


	R^1	R^2
4a	H	H
4b	C_6H_5	H
4c	H	C_6H_5



	R^1	R^2	R^3	R^4
5a	H	H	H	H
5b	C_6H_5	H	H	H
5c	H	C_6H_5	H	H
5d	H	H	C_6H_5	H
5e	H	H	H	CH_3

Scheme 1

The pentafluorophenyl ester monoamides **5a-5e** were prepared from the respective glutaric anhydrides and (methyl)aminoacetaldehyde diethylacetal and subsequent conver-

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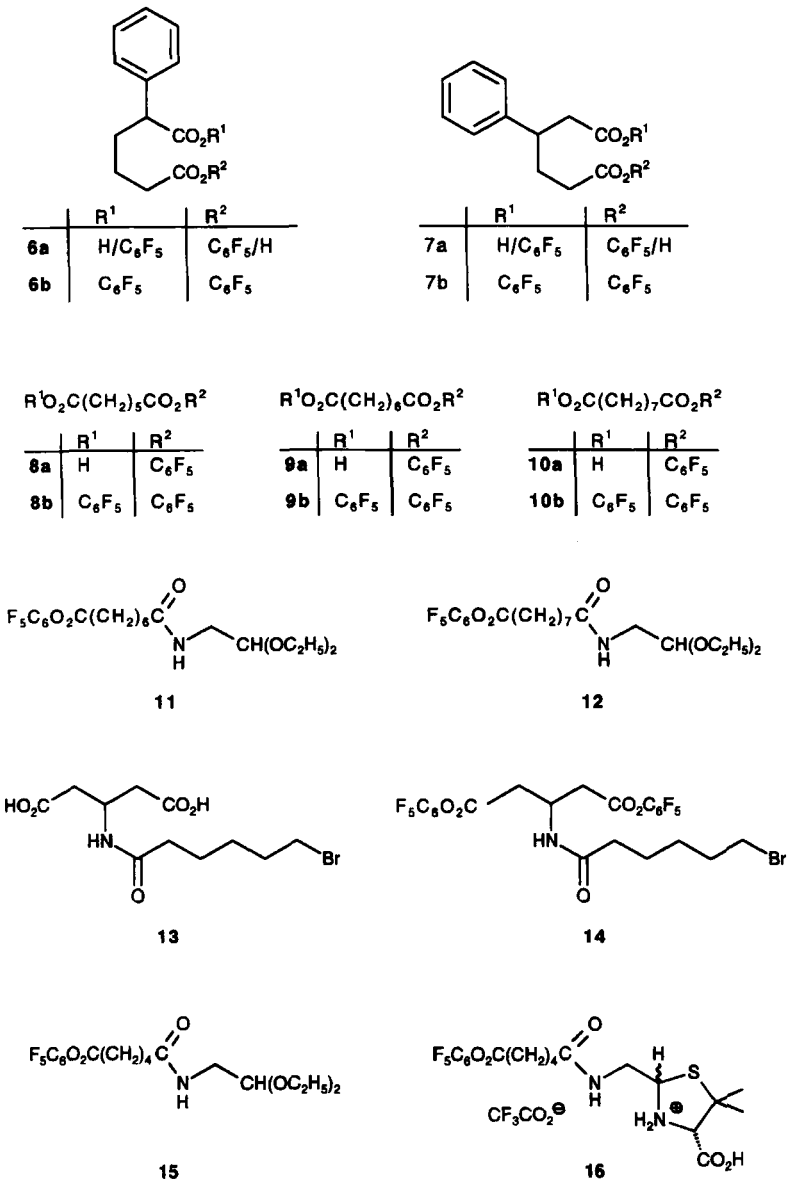

Scheme 2

sion to the ester by the standard procedure (Experim. Part). The homologous ester amides **11** and **12** were prepared in a similar manner, starting from azelaic and suberic acid.

3-Aminoglutaric acid[8] was acylated with 5-bromopentanoic acid chloride to **13** and subsequently converted to the diester **14**. This acid has gained considerable importance recently as a useful starting material in the preparation of carbapenems[9].

Adipic anhydride[10] was reacted with 1-amino-2,2-diethoxyethane to give the ester amide **15**. On treatment with D-(-)-penicillamine in tetrahydrofuran/trifluoroacetic acid, the *O,O*-acetal was converted to the *N,S*-acetal, leading to the exclusive formation of the thiazolidine **16** in very good yield. The pentafluorophenyl ester group was not attacked under these conditions.

In summary, our investigations show the ease of preparation and isolation of pentafluorophenyl esters and have brought forth a number of these esters of important dicarboxylic acids for use in peptide and amide syntheses.

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Experimental Part

M.p. (uncorr.): Dr. Tottoli apparatus (Büchi):- IR: Perkin Elmer 398.- ^{1}H-NMR: Varian T60 (60 MHz), Jeol JNM-FX-100 (100 MHz) and Jeol

JNM-GX-400 (400 MHz).- ^{13}C-NMR: Jeol JNM-FX-100 (25 MHz) and Jeol JNM-GX-400 (100 MHz), δ (ppm).- Mass spectra: Vacuum Generators 7070.

General procedure for the preparation of the pentafluorophenyl esters

10 mmol of the dicarboxylic acid and 10 mmol (half-ester preparation) or 20 mmol (diester preparation) of pentafluorophenol are dissolved in 25 ml of ethyl acetate. The solution is cooled to 0°C, and 10 or 20 mmol of dicyclohexylcarbodiimide are added. After stirring for 5 h, the suspension is filtered and the filtrate evaporated. Purification was accomplished by 'flash' chromatography[3] on silica gel, eluting with hexane/ethyl acetate mixtures, and subsequent recrystallization of solid esters from hexane or ethanol/water (see below). The yield of the diesters **6b-10b** is low since the half-esters were the synthetic goal of those transformations. Working with two equivalents of pentafluorophenol per mol of dicarboxylic acid would have provided the diesters in high yield.

1,4-Bis(pentafluorophenyl)butanedioate (**3**)

3 was eluted with dichloromethane. Yield 3.5 g (77%), m.p. 132°C (ethanol 96%).- IR (KBr): $\tilde{\nu}$ = 1770 cm^{-1} (C=O), 1515 (C=C), 1105 (C-O), 990 (CF).- ^{1}H-NMR ($CDCl_3$): δ = 3.20 (s).- MS (70 eV), m/z (%): 267 (100; M - OC_6F_5)$^+$.- $C_{16}H_4F_{10}O_4$ (450.2) Calcd. C 42.7 H 0.90 Found C 42.4 H 0.89.

1,5-Bis-(pentafluorophenyl)pentanedioate (**4a**)

4a was eluted with hexane/ethyl acetate (7 + 3). Yield 2.9 g (63%), m.p. 66°C (hexane).- IR (KBr): $\tilde{\nu}$ = 1785/1764 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): δ = 2.22 (quint, J = 7 Hz, 2H, 3-CH_2), 2.85 (t, J = 7 Hz, 4H, CH_2CO).- MS (70 eV), m/z (%): 281 (100; M - OC_6F_5)$^+$.- $C_{17}H_6F_{10}O_4$ (464.2) Calcd. C 44.0 H 1.30 Found C 44.2 H 1.40.

1,5-Bis(pentafluorophenyl)2-phenylpentandedioate (**4b**)

4b was eluted with hexane/ethyl acetate (8 + 2). Yield 3.3 g (62%), m.p. 47°C (absol. ethanol).- IR (KBr): $\tilde{\nu}$ = 1774 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): δ = 2.70 (m, 4H, CH_2CH_2), 4.08 (br t, J = 8 Hz, 1H, CH), 7.40 (br s, 5H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 27.8 (CH_2), 30.4 (CH_2), 49.4 (CH), 125.0 (m, 1'-CF), 127.9 (d, $^1J_{CH}$ = 157 Hz, C_6H_5), 128.4 (d, $^1J_{CH}$ = 163 Hz, C_6H_5), 129.3 (d, $^1J_{CH}$ = 159 Hz, C_6H_5), 135.9 (s, 1'-C_6H_5), 137.9 (m, $^1J_{CF}$ = 255 Hz, CF), 139.6 (m, $^1J_{CF}$ = 253 Hz, CF), 141.5 (m, $^1J_{CF}$ = 251 Hz, CF), 168.5 (CO), 169.3 (CO).- MS (70 eV), m/z (%): 357 (28) (M - OC_6F_5)$^+$.- $C_{23}H_{10}F_{10}O_4$ (540.3) Calcd. C 51.1 H 1.87 Found C 50.9 H 1.97.

1,5-Bis(pentafluorophenyl)3-phenylpentanedioate (**4c**)

4c was eluted with hexane/ethyl acetate (8 + 2). Yield 4.0 g (75%), m.p. 88°C (absol. ethanol).- IR (KBr): $\tilde{\nu}$ = 1782 cm^{-1} (CO).- ^{1}H-NMR ($CDCl_3$): δ = 3.15 (d, J = 7 Hz, 4H, CH_2), 3.80 (quint, J = 7 Hz, 1H, CH), 7.32 (br s, 5H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 38.3 (d, $^1J_{CH}$ = 130 Hz, CH), 39.1 (t, $^1J_{CH}$ = 127 Hz, CH_2), 124.9 (t, $^2J_{CF}$ = 27 Hz, CF), 127.1 (d, $^1J_{CH}$ = 159 Hz, C_6H_5), 127.8 (d, $^1J_{CH}$ = 171 Hz, C_6H_5), 129.0 (d, $^1J_{CH}$ = 162 Hz, C_6H_5), 137.9 (td, $^1J_{CF}$ = 248 Hz, $^2J_{CF}$ = 24 Hz, CF), 139.6 (td, $^1J_{CF}$ = 245 Hz, $^2J_{CF}$ = 22 Hz, CF), 140.2 (s, 1'-C_6H_5), 141.0 (md, $^1J_{CF}$ = 254 Hz, CF), 167.2 (CO).- MS (70 eV), m/z (%): 357 (100) (M - OC_6F_5)$^+$.- $C_{23}H_{10}F_{10}O_4$ (540.3) Calcd. C 51.1 H 1.87 Found C 51.0 H 1.88.

N-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-1-butyramide (**5a**)

1.90 g (10 mmol) of glutaric anhydride and 1.45 ml (10 mmol) of 1-amino-2,2-diethoxyethane were stirred in 20 ml of absol. ethanol for 1 h. The solvent was evaporated, and the oily residue was reacted with pentafluorophenol and DCC according to the General Procedure. The ester was purified by cc (hexane/ethyl acetate 1 + 1) (RF = 0.23). Yield 3.47 g (84%), m.p. 59°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3250 (NH), 1784 (COO), 1640 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.20 (t, J = 7 Hz, 6H, CH_3), 2.25 (m, 4H, CH_2CH_2CON), 2.75 (t, J = 6 Hz, 2H, CH_2COO), 3.2-3.8 (m, 6H, CH_2O, CH_2N), 4.48 (t, J = 4 Hz, 1H, CH), 5.90 (br, 1H, NH).- ^{13}C-NMR ($CDCl_3$): δ = 15.3 (CH_3), 20.6 (C-3), 32.4 ($\underline{C}H_2CON$), 34.8 ($\underline{C}H_2COO$), 41.9 (CH_2N), 62.9 (CH_2O), 100.7 (CH), 125.1 (m, $O\underline{C}_6F_5$), 138.0 (md, $^1J_{CF}$ = 263 Hz, CF), 139.7 (md, $^1J_{CF}$ = 251 Hz, CF), 141.0 (md, $^1J_{CF}$ = 254 Hz, CF), 169.2 (COO), 171.8 (CON).- MS (70 eV), m/z (%): 368 (50), (M - OEt)$^+$, 230 (26) (M - OC_6F_5)$^+$, 184 (100), (HOC_6F_5)$^{+\cdot}$.- $C_{17}H_{20}F_5NO_5$ (413.3) Calcd. C 49.4 H 4.88 N 3.4 Found C 49.5 H 4.94 N 3.4.

N-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-2-phenyl-1-butyramide (**5b**)

5b was prepared according to **5a**. The mixture of isomeric esters (2-phenyl, **5b**, and 4-phenyl, **5d**, see below) was separated by cc (hexane/t-butylmethylether 1 + 1).- RF (**5b**) = 0.32. Yield 1.34 g (27%), m.p. 85°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3275 (NH), 1767 (COO), 1635 (CON) cm^{-1}.- The ^{1}H and ^{13}C signals were assigned on the basis of 400 MHz-^{1}H and 100-MHz-^{13}C (fully and 'gated' decoupled; DEPT) and ^{1}H/^{13}C correlation spectra and by comparison with **4a-4c** and **5a** and **5c**: ^{1}H-NMR ($CDCl_3$): δ = 1.07 (t, J = 7 Hz, 3H, CH_3), 1.15 (t, J = 7 Hz, 3H, CH_3), 2.23 (m, 2H, 3-CH_2), 2.61 (m, 2H, CH_2CON), 2.67 (dd, J = 6; 7 Hz, 2H, CH_2COO), 3.25-3.40 (m, 3H, CH_2N and PhC$\underline{H}$), 3.45-3.55 (m, 2H, CH_2O), 3.58-3.68 (m, 2H, CH_2O), 4.41 [t, J = 5 Hz, 1H, C$\underline{H}$(OEt)$_2$], 5.84 (br t, J = 6 Hz, 1H, NH), 7.25-7.40 (m, 5H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 15.3/15.5 (q, $^1J_{CH}$ = 125 Hz, 2 x CH_3), 28.0 (t, $^1J_{CH}$ = 128 Hz, C-3), 31.1 (t, $^1J_{CH}$ = 127 Hz, $\underline{C}H_2COO$), 42.1 (t, $^1J_{CH}$ = 137 Hz, CH_2N), 51.6 (d, $^1J_{CH}$ = 130 Hz, CHPh), 62.8/63.1 (t, $^1J_{CH}$ = 143 Hz, 2 x CH_2O), 100.7 [d, $^1J_{CH}$ = 161 Hz, CH(OEt)$_2$], 125.1 (m, OC_6F_5), 128.2 (d, $^1J_{CH}$ = 155 Hz, C_6H_5), 128.4 (d, $^1J_{CH}$ = 167 Hz, C_6H_5), 129.1 (d, $^1J_{CH}$ = 168 Hz, C_6H_5), 138.1 (md, $^1J_{CF}$ = 257 Hz, CF), 139.4 (s, C_6H_5), 139.6 (md, $^1J_{CF}$ = 251 Hz, CF), 141.5 (md, $^1J_{CF}$ = 263 Hz, CF), 169.2 (s, COO), 172.6 (s, CON).- MS (70 eV), m/z (%): 489 (1), (M$^{+\cdot}$), 444 (22) (M - OC_2H_5)$^+$.- $C_{23}H_{24}F_5NO_5$ (489.4) Calcd. C 56.4 H 4.94 N 2.9 Found C 56.4 H 5.11 N 2.8.

N-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-3-phenyl-1-butyramide (**5c**)

5c was prepared from 3-phenylglutaric anhydride as **5a** and purified by cc (hexane/ethyl acetate 8 + 2). Yield 3.64 g (74%), m.p. 85°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3340 (NH), 1774 (COO), 1638 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.13/1.17 (2xt, J = 7 Hz, 6H, 2 x CH_3), 2.67 (br d, J = 7 Hz, 2H, CH_2CON), 3.0-3.8 (m, 9H, PhCH, CH_2COO, CH_2N, 2 x CH_2O), 4.35 [t, J = 5 Hz, 1H, CH(OEt)$_2$], 5.90 (br, 1H, NH), 7.30 (br s, 5H, Ar-H).- ^{13}C-NMR ($CDCl_3$): δ = 15.4 (CH_3), 39.1 (CHPh), 39.4 ($\underline{C}H_2CO$), 42.2 ($\underline{C}H_2CO$ or CH_2N), 43.0 (CH_2N or $\underline{C}H_2CO$), 62.9 (CH_2O), 63.1 (CH_2O), 100.9 [CH(OEt)$_2$], 125.1 (m, OC_6F_5), 127.4 (C_6H_5), 127.5 (C_6H_5), 129.0 (C_6H_5), 138.2 (md, $^1J_{CF}$ = 250 Hz, CF), 139.8 (md, $^1J_{CF}$ = 253 Hz, CF), 141.5 (md, $^1J_{CF}$ = 262 Hz, CF), 141.9 (C_6H_5), 167.9 (COO), 170.8 (CON).- MS (70 eV), m/z (%): 489 (0.9) (M$^{+\cdot}$), 444 (22) (M - OC_2H_5)$^+$.- $C_{23}H_{24}F_5NO_5$ (489.4) Calcd. C 56.5 H 4.94 N 2.9 Found C 56.6 H 5.04 N 2.7.

N-(2',2'-Diethoxy-1'-ethyl)-4-pentafluorophenyloxycarbonyl-4-phenyl-1-butyramide (**5d**)

For preparation and isolation see **5a**. RF (**5d**) = 0.19. Yield 137 g (28%), m.p. 56°C (pentane).- IR (melt): $\tilde{\nu}$ = 3300 (NH), 1770 (COO), 1650 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$) (cf. **5b**): δ = 1.21 (t, J = 7 Hz, 3H, CH_3), 1.22 (t, J = 7 Hz, 3H, CH_3), 2.15-2.32 (m, 3H, CH_2CH_2), 2.45-2.57 (m,

1H, CH_2CH_2), 3.35-3.48 (m, 2H, CH_2N), 3.50-3.59 (m, 2H, CH_2O), 3.66-3.77 (m, 2H, CH_2O), 4.07 (t, J = 7.5 Hz, 1H, CHPh), 4.51 [t, J = 5 Hz, 1H, $CH(OEt)_2$], 5.83 (br t, J = 6 Hz, 1H, NH), 7.37 (br s, 5H, Ar-H).- ^{13}C-NMR ($CDCl_3$) (cf. **5b**): δ = 15.3 (q, $^1J_{CH}$ = 126 Hz, CH_3), 28.8 (t, $^1J_{CH}$ = 132 Hz, C-3), 33.3 (6, $^1J_{CH}$ = 120 Hz, CH_2CON), 42.0 (t, $^1J_{CH}$ = 137 Hz, CH_2N), 49.9 (d, $^1J_{CH}$ = 140 Hz, CHPh), 63.0 (t, $^1J_{CH}$ = 142 Hz, CH_2O), 100.5 [d, $^1J_{CH}$ = 167 Hz, $CH(OEt)_2$], 125.2 (m, OC_6F_5), 128.1 (d, $^1J_{CH}$ = 164 Hz, C_6H_5), 128.2 (d, $^1J_{CH}$ = 160 Hz, C_6H_5), 129.1 (d, $^1J_{CH}$ = 170 Hz, C_6H_5), 136.7 (s, C_6H_5), 137.7 (md, $^1J_{CF}$ = 251 Hz, CF), 139.2 (md, $^1J_{CF}$ = 254 Hz, CF), 140.8 (md, $^1J_{CF}$ = 263 Hz, CF), 169.9 (s, COO), 171.9 (s, CON).- MS (70 eV), m/z (%): 444 (6) $(M - OC_2H_5)^+$, 103 (100).- $C_{23}H_{24}F_5NO_5$ (489.4) Calcd. C 56.4 H 4.94 N 2.9 Found C 56.5 H 5.06 N 2.8.

N-(2',2'-Diethoxy-1'-ethyl)-N-methyl-4-pentafluorophenyloxycarbonyl-1-butyramide (**5e**)

5e was prepared from glutaric anhydride and N-methylaminoacetaldehyde diethylacetal, and purified by cc (silica gel; hexane/ethyl acetate 1 + 1) to yield 3.40 g (80%) of a pale yellow oil.- IR (film): $\tilde{\nu}$ = 1785 (COO), 1645 (CON) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 1.07 (t, J = 7 Hz, 6H, CH_3), 2.10-2.39 (m, 4H, 2- and 3-CH_2), 2.42-2.65 (m, 2H, CH_2COO), 2.72-3.00 (m, 2H, CH_2N), 3.13 (s, 3H, NCH_3), 3.40-3.85 (m, 4H, CH_2O), 4.57 [t, J = 5 Hz, 1H, $CH(OEt)_2$].- MS (70 eV), m/z (%): 426 (0.3) $(M - H)^+$, 382 (73) $(M - OC_2H_5)^+$.- $C_{18}H_{22}F_5NO_5$ (427.4) Calcd. C 50.6 H 5.19 N 3.3 Found C 50.4 H 5.17 N 3.3.

2-Phenyl-1,6-hexanedioic acid pentafluorophenyl ester (**6a**)

6a was chromatographically separated from the diester (**6b**) (hexane/ethyl acetate 1 + 1; RF = 0.21). Yield of the mixture of isomers (ester group in 1- or 6-position), 1.16 g (30%). The ratio of the isomers was 1:1, as determined by integration of the 2-H signals.- M.p. 83°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3300-2600 (OH), 1786 and 1772 (COOR), 1700 (br, COOH) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 1.60-2.80 (br m, 6H, $CH_2CH_2CH_2$), 3.60 (t, J = 7 Hz, CH of one isomer), 3.90 (t, J = 7 Hz, CH of other isomer), 7.32 (br s, 5H, Ar-H).- MS (70 eV), m/z (%): 388 (0.4) $(M^{+\cdot})$, 205 (38) $(M - OC_6F_5)^+$.- $C_{18}H_{13}F_5O_4$ (388.3) Calcd. C 55.7 H 3.37 Found C 55.7 H 3.67.

1,6-Bis(pentafluorophenyl)2-phenylhexanedioate (**6b**)

Cf. **6a**. RF = 0.83. Yield 0.93 g (17%), m.p. 91°C (absol. ethanol).- IR (KBr): $\tilde{\nu}$ = 1773 cm^{-1} (COOR).- ^1H-NMR ($CDCl_3$): δ = 1.50-2.35 (br, 4H, CH_2CH_2), 2.70 (t, J = 6 Hz, 2H, CH_2CO), 3.93 (t, J = 7 Hz, 1H, CHPh), 7.35 (br s, 5H, Ar-H).- MS (70 eV), m/z (%): 371 (5) $(M - OC_6F_5)^+$, 343 (63) $(M - CO - OC_6F_5)^+$.- $C_{24}H_{12}F_{10}O_4$ (554.3) Calcd. C 52.0 H 2.18 Found C 52.4 H 2.23.

3-Phenyl-1,6-hexanedioic acid pentafluorophenyl ester (**7a**)

7a was chromatographically separated from the diester **7b** (hexane/ethyl acetate 1 + 1; RF = 0.32). Yield of the mixture of isomers (ester group in 1- or 6-position), 1.93 g (50%), m.p. 115°C (hexane);-the ratio of the isomers was 1:1, according to the integrals of the $C\underline{H}_2COOC_6F_5$ protons (see below).- IR (KBr): $\tilde{\nu}$ = 1782 (COOR), 1758 (COOH) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 2.54 (mc, 2 x 1H, $CHC\underline{H}_2CH_2$), 2.70 (mc, 2 x 2H and 2 x 1H, $CHC\underline{H}_2COOH$, $CHCH_2C\underline{H}_2COOH$, and $CHC\underline{H}_2CH_2$), 2.83 (mc, 2H, $CHCH_2C\underline{H}_2COOR$), 3.36 (mc, 1 x 2H and 2 x 1H, $CHC\underline{H}_2COOR$ and Ar-C<u>H</u>), 7.44 (mc, 2 x 5H, Ar-H).- MS (CI, *i*-butane), m/z (%): 388 (1) $(M^{+\cdot})$, 203 (100).- $C_{18}H_{13}F_5O_4$ (388.3) Calcd. C 55.7 H 3.37 Found C 55.7 H 3.20.

1,6-Bis(pentafluorophenyl)3-phenylhexanedioate (**7b**)

Cf. **7a**. RF = 0.76. Yield 0.18 g (3%), m.p. 110-111°C (ethanol 96%).- IR (KBr): $\tilde{\nu}$ = 1775 cm^{-1} (br, CO).- ^1H-NMR ($CDCl_3$): δ= 2.20-2.80 (br m, 3H, CH_2CH), 2.95-3.43 (m, 4H, CH_2CO), 7.33 (br s, 5H, Ar-H).- MS (70 eV), m/z (%): 371 (87) $(M - OC_6F_5)^+$.- $C_{24}H_{12}F_{10}O_4$ (554.3) Calcd. C 52.0 H 2.18 Found C 52.0 H 2.31.

1,7-Heptanedioic acid pentafluorophenyl ester (**8a**)

8a was separated from diester **8b** chromatographically, first eluting the diester with chloroform (RF = 0.82), then the half-ester with chloroform/methanol (9 + 1) (RF = 0.56). Yield 2.00 g (61%), m.p. 66-67°C (ethanol 90%).- IR (KBr): $\tilde{\nu}$ = 3300-2600 (OH), 1779 (COOR), 1695 (COOH) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 1.49 (m, 2H, 4-CH_2), 1.71 (quint, J = 7 Hz, 2H, $C\underline{H}_2CH_2COOH$), 1.81 (quint, J = 7.5 Hz, 2H, $\underline{C}H_2CH_2$ COOR), 2.40 (t, J = 7 Hz, 2H, $C\underline{H}_2COOH$), 2.69 (t, J = 7.5 Hz, 2H, $C\underline{H}_2COOR$).- MS (70 eV), m/z (%): 309 (1) $(M - OH)^+$, 143 (70) $(M - OC_6F_5)^+$.- $C_{13}H_{11}F_5O_4$ (326.2) Calcd. C 47.9 H 3.41 Found C 48.2 H 3.57.

1,7-Bis(pentafluorophenyl)heptanedioate (**8b**)

Cf. **8a**. Yield 1.02 g (21%), m.p. 53-54°C (hexane).- IR (KBr): $\tilde{\nu}$ = 1790 cm^{-1} (CO).- ^1H-NMR ($CDCl_3$): δ = 1.50-2.05 (m, 6H, $CH_2CH_2CH_2$), 2.73 (t, J = 6 Hz, 4H, CH_2COOR).- MS (70 eV), m/z (%): 309 (89) $(M - OC_6F_5)^+$.- $C_{19}H_{10}F_{10}O_4$ (492.3) Calcd. C 46.3 H 2.05 Found C 46.3 H 2.14.

1,8-Octanedioic acid pentafluorophenyl ester (**9a**)

9a was separated from the diester **9b** chromatographically (ethyl acetate: **9a**: Rf = 0.67, **9b**: RF = 0.88). Yield 1.06 g (31%), m.p. 48-51°C (pentane).- IR (KBr): $\tilde{\nu}$ = 3200-2500 (OH), 1783 (COOR), 1705 (COOH) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 1.35-1.50 (m, 4H, 4- and 5-CH_2), 1.67 (quint, J = 7 Hz, 2H, $C\underline{H}_2CH_2COOH$), 1.79 (quint, J = 6.5 Hz, 2H, $C\underline{H}_2CH_2COOR$), 2.38 (t, J = 7 Hz, 2H, CH_2COOH), 2.67 (t, J = 6.5 Hz, 2H, CH_2COOR).- MS (70 eV), m/z (%): 323 (2), $(M - OH)^+$, 157 (100) $(M - OC_6F_5)^+$.- $C_{14}H_{13}F_5O_4$ (340.3) Calcd. C 49.4 H 3.86 Found C 49.3 H 4.01.

1,8-Bis(pentafluorophenyl)octanedioate (**9b**)

Cf. **9a**. Yield 1.42 g (28%), m.p. 76°C (hexane).- IR (KBr): $\tilde{\nu}$ = 1790 cm^{-1} (CO).- ^1H-NMR ($CDCl_3$): δ = 1.37-1.95 [m, 8H, $(CH_2)_4$], 2.70 (t, J = 6.5 Hz, 4H, CH_2COOR).- MS (70 eV), m/z (%): 323 (100) $(M - OC_6F_5)^+$.- $C_{20}H_{12}F_{10}O_4$ (506.3) Calcd. C 47.4 H 2.39 Found C 47.5 H 2.53.

1,9-Nonanedioic acid pentafluorophenyl ester (**10a**)

10a was separated from diester **10b** chromatographically (hexane/ethyl acetate 4 + 6: **10a**: RF = 0.23, **10b**: RF = 0.81). Yield 1.46 g (41%), m.p. 61°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3250-2600 (OH), 1783 (COOR), 1698 (COOH) cm^{-1}.- ^1H-NMR ($CDCl_3$): δ = 1.40 (br s, 6H, 4-, 5- and 6-CH_2), 1.65 (quint, J = 7 Hz, 2H, $C\underline{H}_2CH_2COOH$), 1.78 (quint, J = 7.5 Hz, 2H, $C\underline{H}_2CH_2COOR$), 2.36 (t, J = 7 Hz, 2H, $C\underline{H}_2COOH$), 2.66 (t, J = 7.5 Hz, 2H, CH_2COOR).- MS (70 eV), m/z (%): 337 (4) $(M - OH)^+$, 171 (100) $(M - OC_6F_5)^+$.- $C_{15}H_{15}F_5O_4$ (354.3) Calcd. C 50.9 H 4.27 Found C 50.9 H 4.40.

1,9-Bis(pentafluorophenyl)nonanedioate (**10b**)

Cf. **10a**. Yield 0.70 g (14%), m.p. 41-42°C (hexane).- IR (KBr): $\tilde{\nu}$ = 1788 cm^{-1} (CO).- ^1H-NMR ($CDCl_3$): δ = 1.23-2.05 [br m, 10 H, $(CH_2)_5$], 2.67 (t, J = 6 Hz, 4H, CH_2COOR).- MS (70 eV), m/z (%): 337 (100) $(M - OC_6F_5)^+$.- $C_{21}H_{14}F_{10}O_4$ (520.4) Calcd. C 48.5 H 2.72 Found C 48.5 H 2.71.

N-(2',2'-Diethoxy-1'-ethyl)-7-pentafluorophenyloxycarbonyl-1-heptanoic acid amide (**11**)

11 was prepared in two steps without isolation of the intermediate from octanedioic acid according to **5a**, using THF instead of ethanol as a solvent. **11** was purified chromatographically (hexane/ethyl acetate 1 + 1). Yield 1.0 g (11%), colourless oil.- IR (film): $\tilde{\nu}$ = 3300 (NH), 1790 (COOR), 1640 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.22 (t, J = 7 Hz, 6H, CH_3), 1.42 (br m, 4H, 4- and 5-CH_2), 1.67 (quint, J = 7 Hz, 2H, C$\underline{H}_2$$CH_2$CON), 1.78 (quint, J = 7 Hz, 2H, C$\underline{H}_2$$CH_2$COO), 2.21 (t, J = 7 Hz, 2H, C$\underline{H}_2$CON), 2.66 (t, J = 7 Hz, 2H, C$\underline{H}_2$COO), 3.40 (t, J = 6 Hz, 2H, CH_2N), 3.54 (m, 2H, CH_2O), 3.70 (m, 2H, CH_2O), 4.50 (t, J = 5 Hz, 1H, CH), 5.70 (br s, 1H, NH).- MS (70 eV), m/z (%): 410 (6) (M - OC_2H_5)$^+$, 103 (100).- $C_{20}H_{26}F_5NO_5$ (455.5) Calcd. C 52.7 H 5.77 N 3.1 Found C 52.4 H 5.8 N 3.4.

N-(2',2'-Diethoxy-1'-ethyl)-8-pentafluorophenyloxycarbonyl-1-octanoic acid amide (**12**)

12 was prepared in two steps from nonanedioic acid according to **11**, using DMF instead of THF as a solvent, and purified chromatographically (hexane/ethyl acetate 1 + 1, RF = 0.22). Yield 1.25 g (27%), m.p. 40°C (hexane).- IR (KBr): $\tilde{\nu}$ = 3300 (NH), 1790 (COOR), 1648 (CON) cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ = 1.22 (t, J = 7 Hz, 6H, CH_3), 1.38 (br m, 6H, 4-, 5- and 6-CH_2), 1.65 (quint, J = 7 Hz, 2H, C$\underline{H}_2$$CH_2$CON), 1.77 (quint, J = 7.5 Hz, 2H, C$\underline{H}_2$$CH_2$COOR), 2.20 (t, J = 7 Hz, 2H, CH_2CON), 2.66 (t, J = 7.5 Hz, 2H, CH_2COOR), 3.39 (t, J = 5.5 Hz, 2H, CH_2N), 3.55 (m, 2H, CH_2O), 3.70 (m, 2H, CH_2O), 4.51 (t, J = 5 Hz, 1H, CH), 5.84 (br s, 1H, NH).- MS (70 eV), m/z (%): 424 (7) (M - OC_2H_5)$^+$, 240 (100) (424 - OC_6F_5)$^+$. - $C_{21}H_{28}F_5NO_5$ (469.5) Calcd. C 53.7 H 6.02 N 3.0 Found C 53.6 H 5.88 N 3.3.

N-(6'-Bromo-1'-hexanoyl)-3-amino-1,5-pentanedioic acid (**13**)

553 mg (3.76 mmol) of 3-amino-1,5-pentanedionic acid[8] were dissolved in 3.5 ml of 2M NaOH (= 3.7 mmol) and 3.5 ml of dioxan. 803 mg (3.76 mmol) of 6-bromohexanoic acid in 7.5 ml of dioxan and 3.5 ml of 2M NaOH were added simultaneously within 5 min, keeping the pH > 8. 20 ml of water were added, and the mixture was extracted with three 20-ml portions of ethyl acetate. The aqueous phase was acidified to pH 1-2 with conc. HCl and extracted with four 20-ml portions of ethyl acetate. This extract was dried (Na_2SO_4) and filtered. Evaporation left a solid that was recrystallized from ethyl acetate, yielding 762 mg (63%) of pale yellow crystals, m.p. 117°C.- IR (KBr): $\tilde{\nu}$ = 3350 (NH), 1715 (COOH), 1635 (CON), 1545 (HNCO) cm^{-1}. ^{1}H-NMR (CD_3OD): δ = 1.43-2.01 (m, 6H, $CH_2CH_2CH_2$), 2.19 (t, J = 7 Hz, 2H, CH_2CON), 2.62 (d, J = 6.5 Hz, 4H, C$\underline{H}_2$COOH), 3.43 (t, J = 6.5 Hz, 2H, CH_2Br), 4.52 (br quint, J = 6.5 Hz, 1H, CH), 7.93 (br d, J = 8 Hz, 1H, NH).- MS (70 eV), m/z (%): 277/279 (1), 244 (7) (M - Br)$^+$, 88 (100).- $C_{11}H_{18}BrNO_5$ (324.2) Calcd. C 40.8 H 5.60 N 4.3 Found C 40.9 H 5.62 N 4.3.

1,5-Bis(pentafluorophenyl)N-(6'-bromo-1'-hexanoyl)-3-amino-1,5-pentanedioate (**14**)

14 was prepared from **13** according to the General procedure and purified chromatographically (hexane/ethyl acetate 1 + 1). Yield 5.27 g (80%), m.p. 99-100°C (hexane/ethyl acetate).- IR (KBr): $\tilde{\nu}$ = 3320 (NH), 1787 (COOR), 1656 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.55-1.95 (m, 6H, $CH_2CH_2CH_2$), 2.20 (m, 2H, CH_2CON), 3.05 (d, J = 6 Hz, 4H, CH_2COOR), 3.40 (m, 2H, CH_2Br), 4.67 (m, 1H, CH), 6.20 (br s, 1H, NH).- MS (70 eV), m/z (%): 655/657 (9) ($M^{+\cdot}$), 254 (100).- $C_{23}H_{16}BrF_{10}NO_5$ (656.2) Calcd. C 42.1 H 2.46 N 2.1 Found C 42.0 H 2.49 N 2.1.

N-(2',2'-Diethoxy-1'-ethyl)-5-pentafluorophenyloxycarbonyl-1-pentanoic acid amide (**15**)

15 was prepared in two steps without isolation of the intermediate from adipic anhydride[10] according to **5a**, using dry THF instead of ethanol as a solvent. **15** was purified chromatographically (hexane/ethyl acetate 1 + 1). Yield 3.4 g (80%), m.p. 47-49°C (hexane).- IR (KBr): $\tilde{\nu}$ 3295 (NH), 1783 (COOR), 1640 (CON) cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.22 (t, J = 7 Hz, 6H, CH_3), 1.80 (mc, 4H, CH_2CH_2), 2.28 (t, J = 7 Hz, 2H, C$\underline{H}_2$CON), 2.70 (t, J = 7 Hz, 2H, C$\underline{H}_2$COOR), 3.41 (t, J = 6 Hz, 2H, CH_2N), 3.55 (mc, 2H, CH_2O), 3.71 (mc, 2H, CH_2O), 4.51 [t, J = 5 Hz, 1H, CH(OEt)$_2$], 5.82 (br s, 1H, NH).- ^{13}C-NMR ($CDCl_3$): δ = 15.2 (CH_3), 24.2 (3-CH_2), 24.7 (4-CH_2), 33.0 (C$\underline{H}_2$CON), 35.9 (C$\underline{H}_2$COOR), 41.9 (CH_2N), 62.7 (CH_2O), 62.9 (CH_2O), 100.6 [C$\underline{H}$(OEt)$_2$], 125.1 (m, OC_6F_5), 137.8 (md, $^1J_{CF}$ = 250 Hz, CF), 139.4 (md, $^1J_{CF}$ = 256 Hz, CF), 141.1 (md, $^1J_{CF}$ = 244 Hz, CF), 169.2 (COOR), 172.5 (CON).- MS (70 eV), m/z (%): 382 (15) (M - OEt)$^+$, 103 (100).- $C_{18}H_{22}F_5NO_5$ (427.4) Calcd. C 50.6 H 5.19 N 3.3 Found C 50.4 H 5.20 N 3.5.

2-[N-(5'-Pentafluorophenyloxycarbonyl-1'-pentanoyl)]aminomethyl-5,5-dimethyl-1,3-thiazolinium-4-carboxylic acid trifluoroacetate (**16**)

2.31 g (5.4 mmol) of **15** were dissolved in 40 ml of dry tetrahydrofuran. A solution of 0.81 g (5.4 mmol) of D-(-)-penicillamine in 4.0 ml of tetrahydrofuran and 4.0 ml of trifluoroacetic acid was added and the clear solution stirred at 30-40°C for 36 h. The solvent was evaporated, adding three 5-ml portions of toluene towards the end of the evaporation so as to remove excess trifluoroacetic acid. Diethyl ether (50 ml) precipitated a white powder (consisting of the 2-epimers) on keeping the mixture at 0°C for two weeks; yield 2.81 g (87%), m.p. 89-91°C.- IR (KBr): $\tilde{\nu}$ = 3500-2300, 3340, 1786, 1724, 1667, 1634, 1520, 1200 cm^{-1}.- ^{1}H-NMR ($CDCl_3$): δ = 1.47, 1.51 (br s, 2 x 3H, CH_3), 1.69, 1.70 (br s, 2 x 3H, CH_3), 1.75 (m, 2 x 4H, CH_2CH_2), 2.32 (m, 2 x 2H, CH_2CON), 2.68 (2t, J = 7 Hz, 2 x 2H, CH_2COO), 3.65 (m, 2 x 1H, CH_2N), 3.82 (m, 2 x 1H, CH_2N), 4.27/4.29 (s, 2 x 1H, CHCOO), 5.13 (dd, J = 3; 7 Hz, 1H, CHNS), 5.22 (2d, J = 4; 7 Hz, 1H, CHNS), 7.68 (br t, 1H, NH), 7.76 (br t, 1H, NH), 9.40 (br s, 3H, OH, NH_2).- $C_{21}H_{22}F_8N_2O_7S$ (598.5) Calcd. C 42.1 H 3.71 N 4.7 Found C 41.9 H 3.73 N 4.7.

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