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NEW OPTICALLY RESOLVED PERFLUORO(2-DIALKYLAMINO-PROPIONIC ACIDS)*

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SUMMARY

Optical resolution of several perfluoro(2-dialkylamino-propionic acids) having a perfluorodimethylamino-, a perfluoropyrrolidino-, a perfluoromorpholino- or a perfluoropiperidino-group as the perfluorodialkylamino substituent has been conducted. Among them, those having a perfluorocyclic amino group [a perfluoropyrrolidino-, a perfluoromorpholino- or a perfluoropiperidino-group] were successfully resolved into optically pure (+)- and (−)-perfluoro(2-dialkylamino-propionic acids) via corresponding diastereomeric amides by means of column chromatography. However, in the case of perfluoro(2-dimethylamino-propionic acid), the separation of its diastereomeric amides could not be achieved under the same procedure adopted for those having cyclic amino substituents.

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* As a preliminary report, following paper was presented: E. Hayashi, H. Fukaya, T. Albe and K. Omori, Chem. Lett., (1990) 737.

INTRODUCTION

Optically active compounds such as amines, carboxylic acids, alcohols and epoxides [1] have attracted growing interest for versatile uses, and numerous methodologies have been developed for making them. However, there have been few examples for perfluorinated ones in spite of their potential usefulness as new materials. As an example of a partially fluorinated optically active compound, α-methoxy-α-trifluoromethylphenylacetic acid (MTPA:Mosher reagent) is valuable for the determination of the optical purity of asymmetric compounds [2].

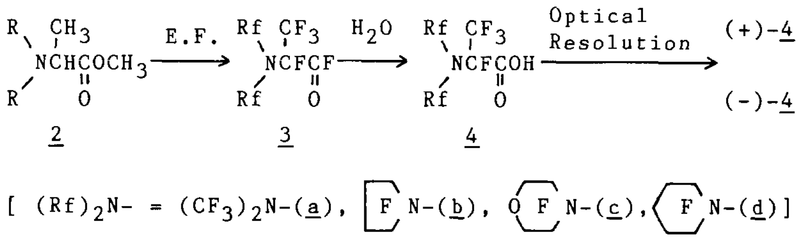
On the other hand, optically active perfluorinated compounds have been considered to have some advantages over non-fluorinated or partially fluorinated ones as chiral agents:(1) no inversion occurs during reactions because of stable C-F bonds,(2) volatile derivatives are formed, for which chromatographic analysis becomes easy,(3) a useful ^{19}F NMR investigation can be applicable, in which the degree of nonequivalence observed for a pair of diastereomeric peaks is usually greater than that in ^{1}H NMR.

An optically active perfluorocarboxylic acid, (+)- and (-)-perfluoro-2-propoxypropionic acid (1)(PPPA), which has the chiral carbon attached to the oxygen atom (perfluoro-propoxy group), has been prepared from the dimerization product of perfluoro-1,2-epoxy-propane by by Kawa and Ishikawa [3].

We have recently obtained various perfluoro(2-dialkylamino-propionyl fluorides)(3) by the electrochemical fluorination of the corresponding methyl 2-dialkylamino-propionates(2).4) Alternatively, perfluoro(2-dimethylamino-

propionates (2) [4]. Alternatively, perfluoro(2-dimethylamino-

synthesized by the reaction of perfluoro-1,2-epoxypropane with $(CF_3)_2N^-$ by Gontar *et al.* [5]. By the hydrolysis of 3, corresponding perfluoro(2-dialkylamino-propionic acids)(4) were easily prepared. As compounds 4 have the chiral carbon attached to the bulky perfluoro-dialkylamino groups, it was



considered that the substitution of the C_3F_7O- group in compound 1 with bulky perfluorodialkylamino groups would provide also new optically active agents having improved efficiency in the separation of diastereomers.

In order to obtain optically pure perfluoro(2-dialkylamino-propionic acids), we first tried to separate diastereomeric amides. However, it was found that the ease of separation into their optically pure forms [5(+)(-) and 6(-)(-)] was affected by the nature of the perfluorodialkylamino group. Then, optically pure (+)- and (-)-perfluoro(2-dialkylamino-propionic acids)[(+)-4 and (-)-4] were prepared by the hydrolysis of the separated amides respectively.

Through these experiments, new optically pure (+)- and (-)-perfluoro(2-pyrrolidino-propionic acid)(4b), perfluoro(2-morpholino-propionic acid)(4c) and perfluoro(2-piperidino-propionic acid)(4d) were obtained successfully. These new optically pure perfluorocarboxylic acids may be used as chiral building blocks, for example, for high performance chiral derivatizing agents with chiral amines and alcohols.

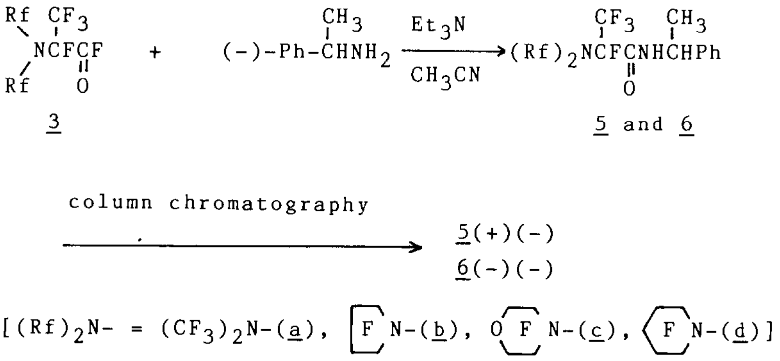
RESULTS AND DISCUSSION

Separation and properties of the diastereomers

The 1:1 mixtures of diastereomeric amides (5 and 6) were obtained quantitatively by the reactions of perfluoro(2-

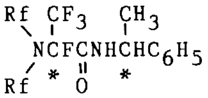
dialkyl-amino-propionyl fluorides)(3) with a mixture of optically pure (-)-1-phenylethylamine and triethylamine in acetonitrile at room temperature.

The pairs of the diastereomeric amides gave generally two distinct spots on silica-gel TLC using hexane - benzene as an eluent except that obtained with perfluoro(2-dimethylamino-propionyl fluoride)(3a). When hexane:benzene =10:3 was used as the eluent, the Rf ratio of the first spots of amides obtained for b, c, and d groups respectively was 0.31, while that of the second spots was 0.41. On the other hand, Rf ratio of the amide from 3a was 0.31-0.33, and was only one spot. This implies the possibility for semigram-separation of the diastereomeric amides from 3b, 3c and 3d by means of chromatography on silica-gel. As expected, the diastereomers of 3b, 3c and 3d were easily separated into each of (+)(-)-isomers(5) and (-)(-)-isomers(6) by column chromatography on silica-gel using hexane-benzene (3:1) as an eluent.



In all cases, the first fractions were (-)(-)-isomers and the second fractions were (+)(-)-isomers. Complete separation of 5a and 6a was not achieved in a similar way.

These separated amides were white crystalline solids. The melting points of (+)(-)-isomers of each pair were higher than those of (-)(-)-isomers. The properties of the resolved amides (5) and (6) are summarized in Table 1.



$$(R_f)_2N\overset{*}{C}F(CF_3)C(=O)NH\overset{*}{C}H(CH_3)C_6H_5$$

TABLE 1

Properties of resolved amides 5 and 6

$(Rf)_2N-$	$[\alpha]_D^{20}(CHCl_3, c\ 1.00)$		m.p (^oC)	
	5	6	5	6
 N- b	-63.1	-69.8	85.0-86.0	57.0-58.0
 N- c	-61.0	-66.6	80.0-81.0	51.5-52.5
 N- d	-62.3	-67.7	72.5-73.5	45.5-47.0

The diastereomeric amides were also analytically separated from each other by means of GLC. Under appropriate conditions (see Experimental section), pairs of the diastereomeric amides were divided with base-line separation. On GLC, (+)(-)-isomers had shorter retention times and (-)(-)-isomers had longer ones; however, the amides 5a and 6a were hardly separated under similar GLC conditions. The successful separation of 5a and 6a was eventually achieved by means of HPLC. The detailed results will be reported in a subsequent paper.

Spectroscopic differences of the diastereomeric amides

These separated amides, 5 and 6 , gave similar absorption patterns in their IR spectra for both diastereomers. The

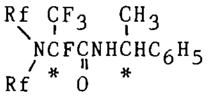
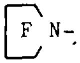
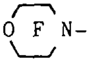
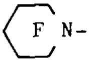

$$(Rf)_2N\overset{*}{C}F(CF_3)C(=O)NH\overset{*}{C}H(CH_3)C_6H_5$$

TABLE 2

Chemical shifts differences due to methine C-F for diastereomeric amides 5 and 6

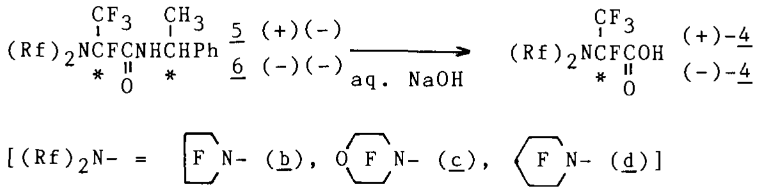
$(Rf)_2N$-	Chemical shifts for methine C-F	
	5	6
$(CF_3)_2N$- a	-136.0	-136.0
 b	———	———
 c	-135.6	-135.4
 d	-136.8	-136.3

corresponding ^1H NMR signals of the diastereomeric pairs also did not exhibit any significant differences. On the other hand, characteristic differences were observed in the ^{19}F NMR spectra between them. In their ^{19}F NMR, differences of absorption peaks were expected to occur both at the α-CF_3 and the methine fluorines directly attached to chiral carbons. In the case of diastereomeric derivatives of PPPA [3,6] and MTPA [2], greater chemical shift differences due to CF_3 at α-positions than those observed for these methine fluorines were reported. On the other hand, in the cases of 5 and 6, it was found that only the signals from the methine fluorines were differentiated, not those from α-CF_3. The differences in the ^{19}F NMR chemical shifts due to the methine C-F are shown in Table 2. The chemical shift difference observed for perfluoropiperidino derivatives (5d and 6d) was enough to calculate the mixture ratio of the diastereomers (Fig. 1).

The value of the chemical shift difference was strongly affected by the kind of solvent used. Generally, polar solvents gave larger differences for signals from each diastereomer. For example, in the case of perfluoro-piperidino derivatives(5d and 6d), the value of difference was 0.17ppm in benzene, while in acetone this value was 0.75ppm. In the case of morpholino derivatives(5c and 6c), such differences were from almost 0ppm(in benzene) to 0.29ppm(in acetone) although in all solvents the separation was not complete.

Unfortunately, in the case of pyrrolidino derivatives(5b and 6b), the signals of the methine fluorines overlapped with one of the peaks of the AB pattern (-135.6 ppm,J=250Hz) for the β-CF_2's of the perfluoropyrrolidino group, and the value of differences could not be determined exactly (Fig. 2).

Hydrolysis of the separated amides



$$(Rf)_2N\overset{CF_3}{\underset{*}{C}}F\underset{\|\atop O}{C}NH\overset{CH_3}{\underset{*}{C}}HPh \quad \begin{matrix}5\ (+)(-)\\ 6\ (-)(-)\end{matrix} \xrightarrow[\text{aq. NaOH}]{} (Rf)_2N\overset{CF_3}{\underset{*}{C}}F\underset{\|\atop O}{C}OH \quad \begin{matrix}(+)\text{-}4\\ (-)\text{-}4\end{matrix}$$

The separated amides were hydrolyzed with sodium hydroxide and the optically active(optically pure)(+)- and (-) -perfluoro-(2-dialkylamino-propionic acids)[(+)-4 and (-)-4] were obtained in yields of 60-70% respectively by distillation with concentrated sulfuric acid.

The properties of (+)-4 (+ isomers) and (-)-4 (- isomers) are summarized in Table 3.

These optically active perfluorocarboxylic acids are, as far as we know, the first examples of the optically resolved perfluorinated carboxylic acids obtained via electrochemical fluorination.

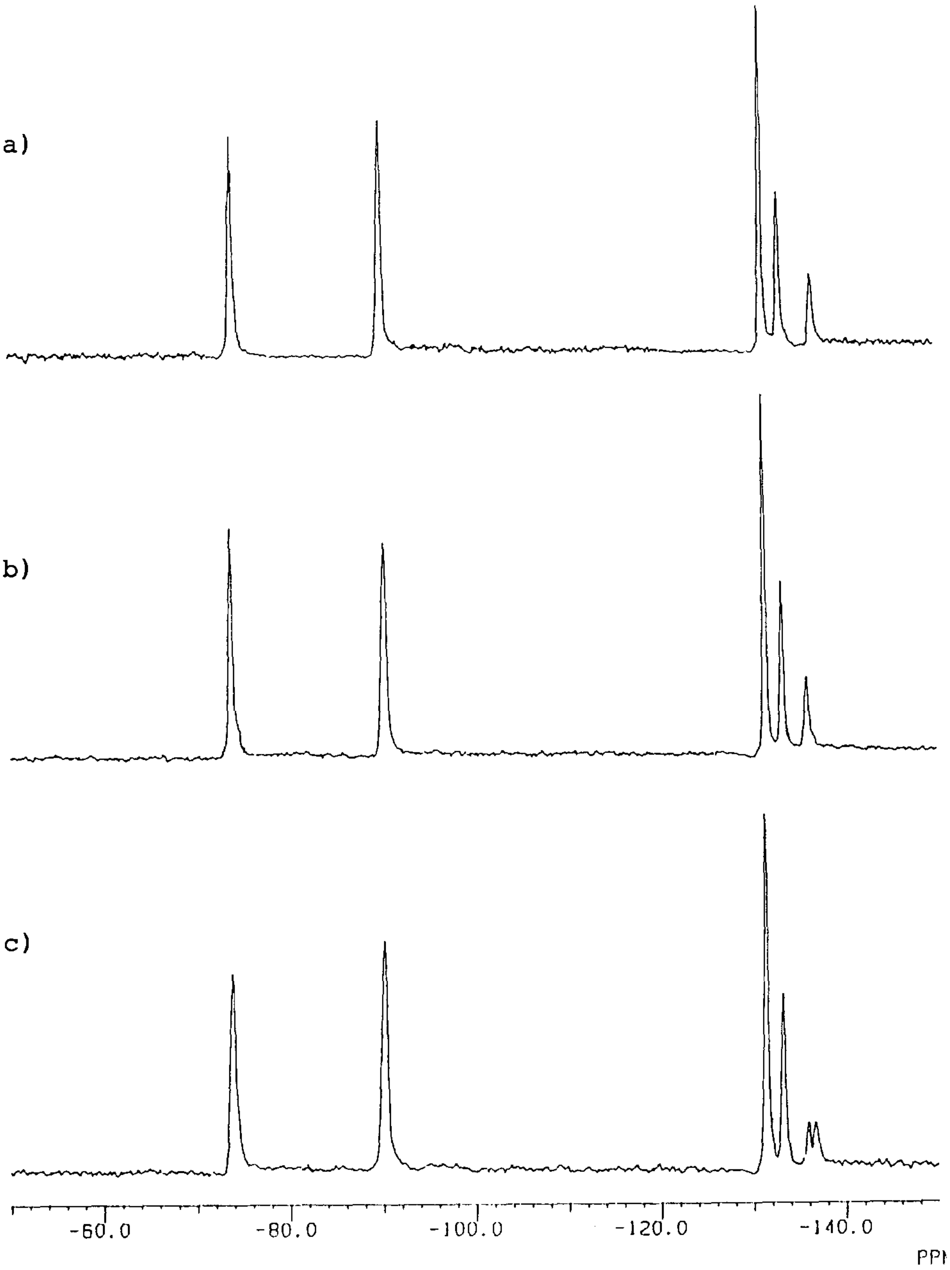


Fig. 1. ^{19}F NMR spectra of diastereomeric amides 5d and 6d; a) ^{19}F NMR spectrum of 5d; b) ^{19}F NMR spectrum of 6d; c) ^{19}F NMR spectrum of 50:50 mixture of 5d and 6d.

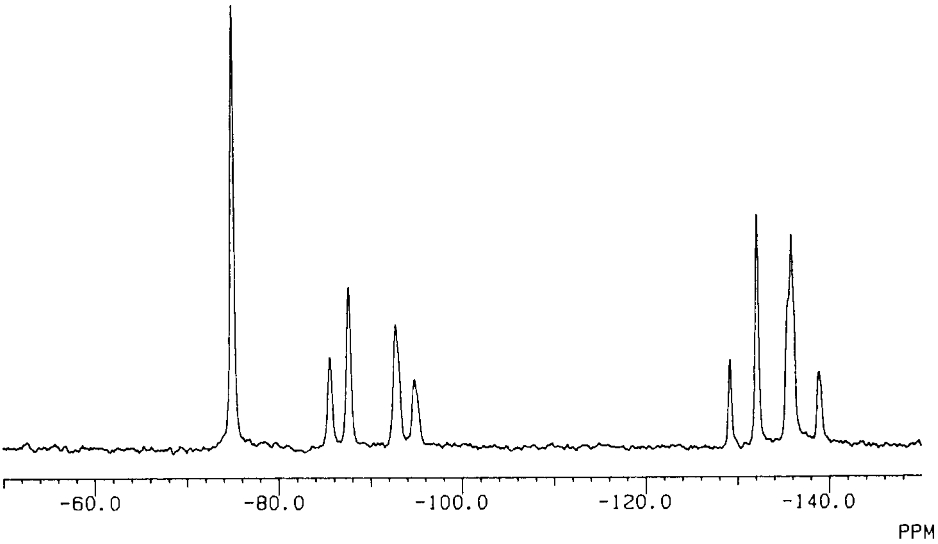


Fig. 2. ^{19}F NMR spectrum of 50:50 mixture of 5b and 6b.

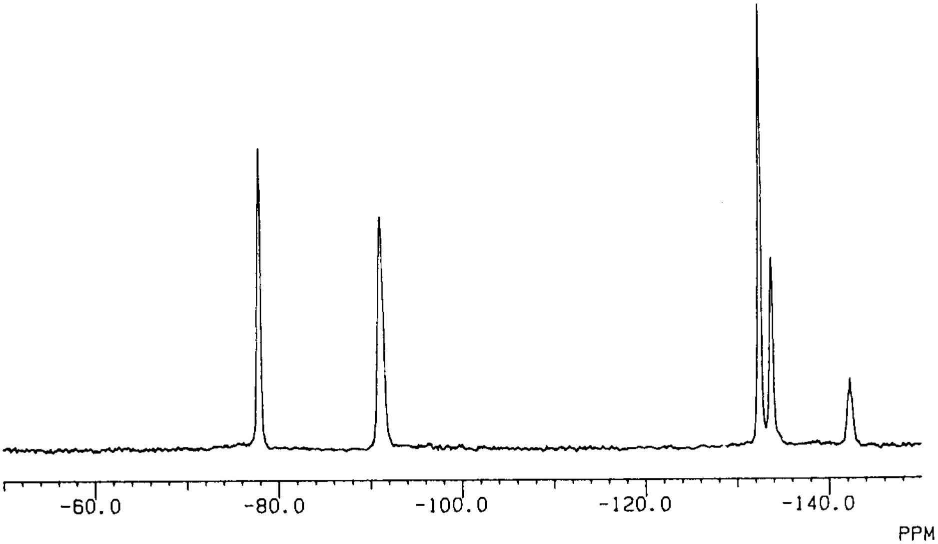
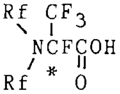


Fig. 3. ^{19}F NMR spectrum of perfluoro(2-piperidinopropionic acid) (4d).

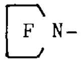


$(Rf)_2N\overset{*}{C}F(CF_3)COOH$

(+)-4 ;(+)-isomer
(-)-4 ;(-)-isomer

TABLE 3

Properties of optically pure (+)-4 and (-)-4

$(Rf)_2N-$	$[\alpha]_D^{20}(CHCl_3, c\ 1.00)$		b.p (^oC/torr)	
	(+)-4	(-)-4	(+)-4	(-)4
 b	13.0	-13.0	70.0-72.0/36	
 c	16.0	-16.0	75.0-77.0/35	
 d	14.5	-14.4	78.0-80.8/35	

EXPERIMENTAL

Apparatus

Optical rotations were measured with a JASCO DIP-370 spectrometer using a quartz cell (3mm X 100mm). IR spectra were recorded on a Hitachi EPI-G3 spectrometer. ^1H NMR spectra were measured on 5% solutions in $CDCl_3$ using $SiMe_4$ as internal standard and were recorded on a Hitachi R-90H (90.01MHz) spectrometer. ^{19}F NMR spectra were measured on 5% solutions in $CDCl_3$ using CCl_3F as internal standard on a Hitachi R-90F (84.68MHz) spectrometer.

GLC analysis was carried out on a Shimadzu GC-6A using a stainless column (3mm X 3.0m) packed with 10% Thermol III on Uniport B (60-80 mesh). The carrier gas was helium. The column was kept at 160 ^oC.

TLC analysis was carried out using aluminum sheets precoated with 0.2 mm thick silica gel $60F^{254}$(Merk).

Starting Materials

The perfluoro(2-dialkylamino-propionyl fluorides) used were all made by the electrochemical fluorination of the corresponding methyl 2-dialkylamino-propionic acids. [4].

(-)-1-Phenylethylamine(Wako Chemical Ltd.) was used as received.

Preparation and resolution of diastereomeric amides

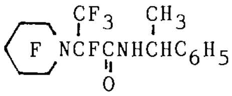
To illustrate a typical example of these procedures, the piperidino derivatives will be described.

To a solution of (-)-phenylethylamine (2.80 g, 23.2 mmol) and triethylamine(2.42 g, 24.0 mmol) in 10 ml of acetonitrile, perfluoro(2-piperidino-propionyl fluoride)(2d)(9.25 g, 22.5 mmol) was added at room temperature. After 2 hr. standing, the solvent was evaporated under reduced pressure. The residue was dissolved in 2N HCl (50 ml) and extracted with ether (25 ml x 2). The ether solution was washed with 1N $NaHCO_3$ and water, and dried over $MgSO_4$. After evaporation of the solvent, pure 1:1 mixture of diastereomeric amides was obtained (10.95 g, 21.4 mmol, 92% yield).

The mixture (1.0 g)(5d and 6d) was separated by silica gel column chromatography (2 cm X 50 cm, Wako gel C-200) using hexane-benzene (10:3) as an eluent to give crude (-)(-)-isomer(0.45 g) and crude (+)(-)-isomer(0.39 g). Similar work-up was carried out several times and 3.5 g of crude

(-)(-)-isomer and 3.0g of crude (+)(-)-isomer were obtained. These crude isomers were purified respectively by further silica gel chromatography[2 cm X 75 cm, Wako gel C-300, hexane-benzene(4:1)]. Thus, better than 98% pure (from GLC analysis) (+)(-)-isomer(5d)(2.5 g) and (-)(-)-isomer(6d) (2.3 g) were obtained.

(5d)(+)(-)-isomer (nc):



$\mathrm{F}\;\mathrm{N}\overset{\overset{CF_3}{|}}{\mathrm{C}}\mathrm{F}\underset{\underset{O}{\|}}{\mathrm{C}}\mathrm{NH}\overset{\overset{CH_3}{|}}{\mathrm{C}}\mathrm{H}C_6H_5$

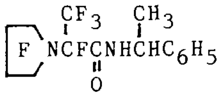
$[\alpha]_D^{20}$, -62.3; m.p., 72.5-73.5°C. IR(cm^{-1}),3342(NH), 1699(C=O). ^1H NMR(δ);1.56(CH_3),5.56(CH),6.63(NH), 7.32(C_6H_5). ^{19}F NMR(δ);-74.6(CF_3),-91.8(CF_2),-132.4(CF_2), -134.3(CF_2),-136.8(CF).

(6d)(-)(-)-isomer (nc):

$[\alpha]_D^{20}$, -67.7; m.p., 45.5-47.0°C. IR and ^1H NMR spectra were similar with (+)(-)-isomer. ^{19}F NMR(δ);-74.5(CF_3), -136.3(CF), other peaks were similar to those of the (+)(-)-isomer.

Among the diastereomeric amides, each pair of the perfluoropyrrolidino- and perfluoromorpholino-derivatives were separated in a similar way, and **satisfactorily purified** (better than 98%) (+)(-)- and (-)(-)-isomers were obtained.

(5b)(+)(-)-isomer (nc):



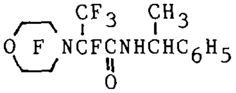
$\mathrm{F}\;\mathrm{N}\overset{\overset{CF_3}{|}}{\mathrm{C}}\mathrm{F}\underset{\underset{O}{\|}}{\mathrm{C}}\mathrm{NH}\overset{\overset{CH_3}{|}}{\mathrm{C}}\mathrm{H}C_6H_5$

$[\alpha]_D^{20}$,-63.1; m.p., 85.0-86.0°C. IR(cm^{-1});3377(NH), 1702(C=O). ^1H NMR(δ);1.53(CH_3),5.18(CH),6.63(NH),7.32(C_6H_5). ^{19}F NMR(δ);-74.7(CF_3),-88.1(CF_2) and -92.7(CF_2)(AB pattern J=175),-132.1(CF_2) and -136.1(CF_2)(AB pattern J=250), -135.8(CF).

(6b)(-)(-)-isomer (nc):

$[\alpha]_D^{20}$, -69.8; m.p., 57.0-58.0°C. IR and ^1H NMR spectra were similar with (+)(-)-isomer. ^{19}F NMR(δ);-74.7(CF_3), -88.1(CF_2) and -92.7(CF_2)(AB pattern J=175),-132.1(CF_2) and -136.3(CF_2)(AB pattern J=272),-136.0(CF).

(5c)(+)(-)-isomer (nc):



$$\text{O}\;\;\text{F}\;\;\text{N}\overset{\text{CF}_3}{\text{C}}\text{F}\underset{\substack{\| \\ \text{O}}}{\text{C}}\text{NH}\overset{\text{CH}_3}{\text{C}}\text{HC}_6\text{H}_5$$

$[\alpha]_D^{20}$, -61.0; m.p., 80.0-81.0°C. IR(cm^{-1});3334(NH), 1700(C=O). ^1H NMR(δ)1.56(CH_3),5.56(CH),6.63(NH),7.32(C_6H_5). ^{19}F NMR(δ);-74.8(CF_3),-84.4(CF_2) and -88.1(CF_2)(AB pattern J=148),-87.8(CF_2) and -92.7(CF_2)(AB pattern J=198),-135.6(CF).

(6c)(-)(-)-isomer (nc):

$[\alpha]_D^{20}$, -66.6; m.p., 51.5-52.5°C. IR and ^1H NMR spectra were similar with (+)(-)-isomer. ^{19}F NMR(δ);-135.4(CF), other peaks were similar to those of the (+)(-)-isomer.

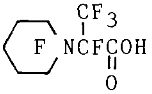
The diastereomeric amides from perfluorodimethylamino derivatives(5a and 6a) could not be separated from each other in a similar way. So, further investigation was not carried out.

Hydrolysis of the separated amides

This procedure was similar to the method described in the patent by Ishikawa [7]. To illustrate these procedures, the example of piperidino derivatives(5d) will be described.

To 2.1g of 5d, 1.0 ml of conc. H_2SO_4 was added and stirred for 1 hr. at room temperature. The reaction mixture was dissolved with 30 ml of water containing ice. Separated oily layer was extracted with ether (5 ml X 3). After the ether was evaporated, 4.0 ml of 6N NaOH solution was added to residue. The solution was refluxed for 2hr. After the reaction mixture was acidified with 6N HCl, the separated oily layer was extracted with ether (5 ml X 3). The ether solution was dried over $MgSO_4$. After ether was evaporated, 1.0 ml of conc. H_2SO_4 was added to the solution. By evaporating at reduced pressure, 1.2 g of the carboxylic acid (<u>4d</u>) was obtained.

(+)-Perfluoro(2-piperidino-propionic acid)(+)-(<u>4d</u>) (nc):



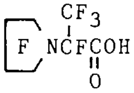
$[\alpha]_D^{20}$, 14.5; b.p., 78.0-80.0 °C/35torr. IR(cm^{-1});1780 (C=O). ^1H NMR(δ);10.2(COOH). ^{19}F NMR(δ);-76.5(CF_3),-90.8 (CF_2),-132.2(CF_2),-133.7(CF_2),-141.0(CF)(See Fig.3). Found: C,23.40%. Calculated for $C_8F_{14}NO_2H$: C,23.49%.

(-)-Perfluoro(2-piperidino-propionic acid)(-)-(<u>4d</u>) (nc):

$[\alpha]_D^{20}$, -14.4; b.p., 78.0-80.0°C/35torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C,23.39%. Calculated for $C_8F_{14}NO_2H$:C,23.49%.

By similar ways, optically pure perfluoro(2-pyrrolidino-propionic acid) and perfluoro(2-morpholino-propionic acid) were respectively obtained.

(+)-Perfluoro(2-pyrrolidino-propionic acid)(+)-(<u>4b</u>) (nc):

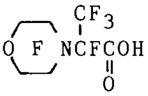


$[\alpha]_D^{20}$, 13.0; b.p., 70.0-72.0°C/35torr. IR(cm^{-1});1780 (C=O). ^1H NMR(δ);10.2(COOH). ^{19}F NMR(δ);-76.0(CF_3),-89.2 (CF_2) and -92.4(CF_2)(AB pattern J=172),-132.8(CF_2) and -135.6 (CF_2)(AB pattern J=250),-135.9(CF). Found:C,23.31%. Calculated for $C_7F_{12}NO_2H$:C,23.41%.

(-)-Perfluoro(2-pyrrolidino-propionic acid)(-)-(<u>4b</u>) (nc):

$[\alpha]_D^{20}$, -13.0; b.p., 70.0-72.0°C/35torr. IR, ^1H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C, 23.32%. Calculated for $C_7F_{12}NO_2H$: C,23.41%.

(+)-Perfluoro(2-morpholino-propionic acid)(+)-(4c) (nc):



$[\alpha]_D^{20}$, 15.9; b.p., 75.0-77.0°C/35torr. IR(cm^{-1});1780 (C=O). ^{1}H NMR(δ); 10.2(COOH). ^{19}F NMR(δ);-76.5(CF_3),-84.4 (CF_2) and -88.1(CF_2)(AB pattern J=148),-87.8(CF_2) and -92.7(CF_2) (AB pattern J=198),-141.2(CF). Found:C,22.30%. Calculated for $C_7F_{12}NO_3H$: C,22.41%.

(-)-Perfluoro(2-morpholino-propionic acid)(-)-(4c) (nc):

$[\alpha]_D^{20}$, -16.0; b.p., 75.0-77.0°C/35torr. IR, ^{1}H NMR and ^{19}F NMR spectra were identical with (+)-isomer. Found:C, 22.23%. Calculated for $C_7F_{12}NO_3H$: C,22.41%.

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