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SYNTHESIS OF PERFLUOROCHEMICALS FOR USE AS BLOOD SUBSTITUTES. PART IV. ELECTROCHEMICAL FLUORINATION OF N-CYCLOALKYL-PYRROLIDINES AND -PIPERIDINES

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SUMMARY

Electrochemical fluorination of N-cyclopentylpyrrolidine gave the corresponding F-amine together with a ring-opened compound N-(F-pentyl)-F-pyrrolidine in the ratio of 1 to 1, in 55% yield. N-cyclohexylpyrrolidine, N-cyclopentylpiperidine, and N-cyclohexylpiperidine were also electrochemically fluorinated in the same manner to give the corresponding F-amines, their isomers with rearranged structures, and ring-opened ones, in the ratio of ca. 4:2:1, 2:1:1, and 2:1:1, respectively in 51 to 53% yields. Supporting spectral data are presented.

INTRODUCTION

Previous work [1] on perfluorochemical oxygen-transport emulsions [2] has shown that acyclic F-tert-amines exhibit longer dwelling times in the reticuloendothelial organs compared to monocyclic analogues. It is, therefore, of interest to prepare bicyclic F-tert-amines to see if they show a greater excretion rate in comparison with monocyclic analogues [3,4]. For the preparation of such F-chemicals electrochemical fluorination seems to be the most promising technique [5], but relatively little attention has been paid for the application of this technique to the bicyclic tert-amine substrates [6-9].

This paper describes the synthesis of N-(F-cycloalkyl)-F-pyrrolidines and N-(F-cycloalkyl)-F-piperidines by electrochemical fluorination.

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RESULTS AND DISCUSSION

The substrates N-cyclopentylpyrrolidine (1), N-cyclohexylpyrrolidine (2), N-cyclopentylpiperidine (3), and N-cyclohexylpiperidine (4) were synthesized from the corresponding cyclic amines (pyrrolidine and piperidine) and cyclic ketones (cyclopentanone and cyclohexanone) through a well-known enamine formation reaction followed by reduction with formic acid [10]. Electrocheminal fluorinations of 1-4 were conducted by the conventional way described elsewhere [5]. The electrochemical fluorination of these substrates proceeded smoothly and gave the crude fluorinated products in 74-78% yields when calculated assuming the products obtained were all desired.

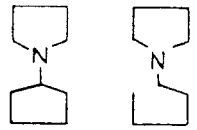
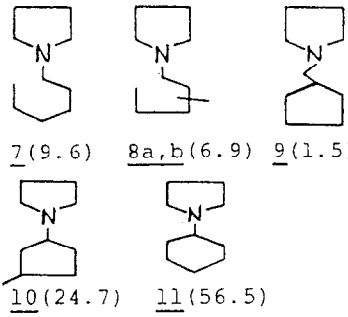
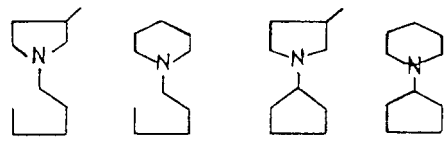
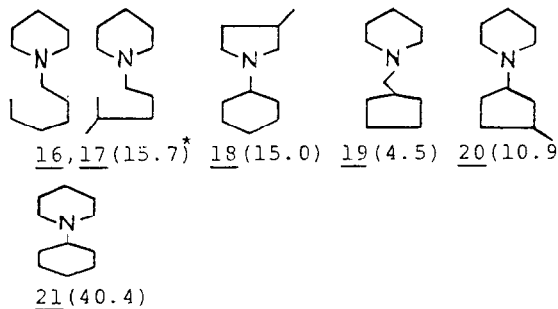
Since our concern is the preparation of perfluorochemicals useful as oxygen carriers, the fragmented products which have less carbon atoms than those of the starting substrates and the polyfluorinated or N-F bond-containing products which often have a fatal toxicity were omitted from our study on the products. For our restricted purpose, the crude fluorination products were at first treated with a mixture of 8N aqueous sodium hydroxide and diisobutylamine to remove not-fully-fluorinated by-products and then with a potassium iodide-acetone solution to remove any contaminating nitrogen fluorides. After the treatment the yields of the perfluorinated products decreased to 51-55%. The perfluorinated product thus obtained was usually a mixture of the structural isomers so that the isolation of each component was difficult even by careful distillation using a spinning band column. The pure sample of each component was, therefore, isolated by repeated collection using preparative scale gas chromatography and analyzed by F-NMR.

The results of the electrochemical fluorinations of 1-4 are summarized in Table I. The percentages of the desired perfluorinated products with the corresponding bicyclic structures 1-4 in the multi-component mixtures were 40-57% (by g.l.c.) due to the formation of various kinds of degraded and rearranged by-products.

Perfluorinated products obtained by the electrochemical fluorination of 1 consisted of the desired N-(F-cyclopentyl)-F-pyrrolidine 5 and a ring-opened N-(F-n-pentyl)-F-pyrrolidine, 6 (1:1, 55% yield). Both structures were unequivocally assigned by the ^{19}F-NMR spectra of the pure samples collected by g.l.c. (Table II). Carbon-nitrogen bond scission generally occurs in the fluorination process leading to the formation of the nitrogen

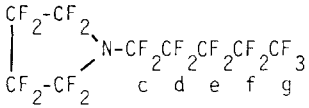
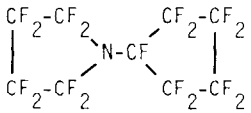
TABLE I

Product distribution of F-tert-amines obtained by the electrochemical fluorination of 1 - 4

Substrate	Yield(%) Crude	Yield(%) After treatment	Product distribution (%)
1	76	55	 5(52.5) 6(46.4)
2	76	53	 7(9.6) 8a,b(6.9) 9(1.5) 10(24.7) 11(56.5)
3	78	51	 12(6.0) 13(19.1) 14(21.3) 15(45.3)
4	74	52	 16,17(15.7)* 18(15.0) 19(4.5) 20(10.9) 21(40.4)

*16:17=8:1 Product distribution was calculated by glc peak areas. All unmarked positions are bonds to fluorine.

TABLE II
^{19}F-NMR spectra of products 5 and 6

Compound		Chemical shift[1]		J(Hz)
5		a	135.1(4F)	
		b	92.1(4F)	b-c = 11.3
		c	93.7	
		d	124.0	d-f = 14.7
		e	124.0	e-g = 9.0
		f	128.0	f-g = 3.3
		g	82.7	
6		a	135.5(4F)	b-c = 12.7
		b	92.4(4F)	c-d = 11.3
		c	141.5	
		d	117.6(2F)	J_{AB} = 254
			135.4(2F)	
		e	126.3(2F)	J_{AB} = 243
			133.3(2F)	

[1] Values in ppm relative to internal $CFCl_3$; Relative peak intensities were correct.

fluoride derivatives, but these by-products were chemically eliminated before the analysis and to what extent this kind of scission occurred was not established in this study. Since the ring contraction of a five-membered ring to a smaller one was very unlikely to occur and to our knowledge at least there have been no such reports, the possible by-products expected from this 5-5 ring structure arise only from the ring-opening reaction. It is very interesting that there was found only one by-product, which arose from C-C bond scission in the cyclopentane ring but not in the pyrrolidine ring. This will be discussed later in connection with the by-products analysis of the other substrate cases.

Gas chromatogram of the electrochemical fluorination products of 2 (measured on column C at an oven temperature of 50°C) showed 5 peaks of compounds 7-11 at 7.32, 7.52, 8.19, 8.82, and 9.24 minutes, respectively.

Mass spectra of the compounds 7, 8 and 9 had m/z 264 F- $\square\overset{+}{N}=$ as the base peak, supporting the existence of the pyrrolidine ring in their structures. The highest m/z (514) observed in the mass spectra of 7 and 8 and m/z 476 observed in those of 9 and 10 seemed to be $M\text{-}F^+$ for which structural formulae were $C_{10}F_{20}N$ and $C_{10}F_{18}N$, respectively. The mass spectra of 11 showed M^+ at m/z 495. These data suggested that 7 and 8 had monocyclic structures and that 9, 10, and 11 had bicyclic ones. These mass spectral data were consistent with the structures shown in Table III which were established by their F-NMR spectra except for 9 which was based only on its mass spectrum.

Two signals observed at 185.7 and 186.7 ppm in the F-NMR spectrum of 8 in the intensity ratio of 3 to 8 suggested that there were two components, each of which had a differently branched hexyl chain. All the signals of 8 were elucidated by the superimposition of the structures of 8a and 8b in the ratio of 3 to 8. Some more detailed explanation for the interpretation of the ^{19}F-NMR spectra should be made here on 8a, 8b, and 10, because the determination of the CF_3 branch position is so delicate. 8b showed two identical CF_3 groups (72.6 ppm) so that confidently assigned is the F-isohexyl group. The compound 8a has two CF_3 groups with different chemical shifts (71.4 and 80.8 ppm), suggesting the former is connected to a tertiary carbon and the latter to a secondary one. Possible structures are F-sec-hexyl, F-2-methylpentyl, and F-3-methylpentyl. The ^{19}F-NMR data were not fully explained by the first and the second structures; 185 and 92.8 ppm observed in ^{19}F-NMR spectrum of 8a are too high for $\rangle$N-CF$\langle$ and $\rangle$N-$CF_2CF\langle$, respectively. Only the third one is consistent with all the data. The structure of 10 is easily determined as N-(F-methylcyclopentyl)-F-pyrrolidine by analogy, but the CF_3 position at the cyclopentane ring is somewhat difficult to allocate. Two possible structures (A) and (B) are shown in Fig. 1.

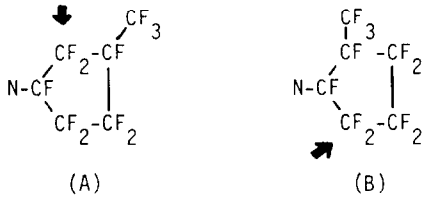
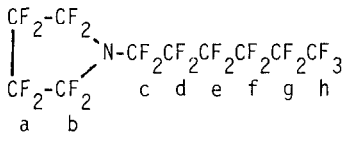
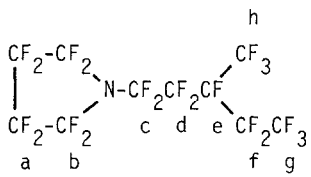
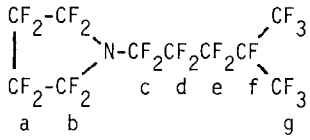


Fig. 1. Possible structures of the F-methylcyclopentyl group of 10.

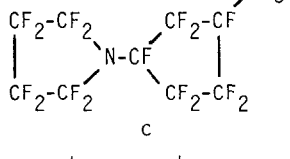
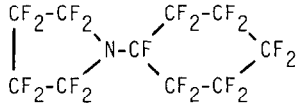
TABLE III

^{19}F-NMR spectra of products 7, 8a, 8b, 10, and 11

Compound		^{1} Chemical shift
7		a 132.5(4F) b 90.5(4F) c 92.5 d-f 122.5(6F) g 126.0 h 81.2
8a		a 133.4(4F) b 91.1(4F) c 92.8 d 113.5 e 185.7 f 117.1 g 80.8 h 71.4
8b		a 133.4(4F) b 91.1(4F) c 92.8 d 122.0 e 115.5 f 186.7 g 72.6(6F)

(Continued)

TABLE III (cont.)

10		a	133.5(4F)
		b	91.1(4F)
		c	140.5
		d	109.0(1F)
			127.3(1F)
		e	182.3
		f	73.7
		g	123.3(1F)
			138.0(1F)
		h	119.8(1F)
			135.0(1F)
11		a	132.6(4F)
		b	87.6(4F)
		c	160.0
		d	120.3(2F) J_{AB} = 260
			134.6(2F)
		e	122.6(2F)
			139.2(2F)
		f	123.3(2F) J_{AB} = 280
			142.2(2F)

[1] Values in ppm relative to internal $CFCl_3$. Only apparent coupling constants were given. Relative peak intensities were correct.

Both structures are consistent with 73.7 ppm of CF_3, but 109.0 and 127.3 ppm of CF_2 seem to be too low for the arrowed CF_2 group of (B), giving a clue for differentiating them. Chemical shift of $-CF_i CF_2 CF_j-$ is very sensitive to adjacent fluorine numbers i and j. The smaller the i+j value the lower is the chemical shift [11]. The chemical shifts of the corresponding CF_2 in the F-cyclopentyl group of 14 and 15 were ca. 117 and 132 ppm. In our experience about 5 ppm downward shift occurs by the substitution of F with CF_3 which corresponds to the decrease of i+j by one. Since i+j decreases in (A) by one but does not change in (B), the estimated chemical shifts of the CF_2 concerned are 112 and 127 ppm for (A) which are very close to the values observed in the spectrum of 10. Based on the above discussion the structure of 10 was assigned as shown in Table III. As was found in the electrochemical fluorination of 1, the ring-opening reaction occurred only in the cyclohexyl ring but not in the pyrrolidine one.

The perfluorinated products obtained by fluorination of 3 consisted of four major components 12 to 15. The highest mass (m/z 514) found in the mass spectra of 12 and 13, which are very likely to be M-F, suggested that 12 and 13 had structures with the piperidine or cyclopentane rings opened. The fragment ions of m/z 314 with high relative intensities, 96.4 for 12 and 100 for 13, suggested that there existed such moieties as F-  or F-  and hence 12 and 13 were N-(F-pentyl)-F-piperidine or N-(F-pentyl)-(F-methyl)-F-pyrrolidine. This kind of an alpha cleavage is generally observed in the mass spectrum of an F-tert-alkylamine $^1R^2R^3RN$ as well as the hydrocarbon counterpart. Other fragment ions formed by cleavage, $^mR^nRN^+=CF_2$ (m=n, $1 \leq m,n \leq 3$) gave useful structural information. Especially, such fragment ions as $(\underbrace{CF_2)_n}N^+=CF_2$ (n=4,5) are rather high in relative intensity and hence diagnostic for the cyclic amine structures unless a branched R_F group is located at the flanked positions of the N atom, in which case alpha cleavage predominantly occurred at the branched R_F group due to a steric hindrance [12]. ^{19}F-NMR of 12 showed two CF_3s at 74.3 and 82.4 ppm, a CF at 184.6 ppm, 2 cyclic CF_2 adjacent to nitrogen at 80-100 ppm (AB quartet), a CF_2 at 125-131 ppm (AB quartet), CF_2 at 82.5 ppm adjacent to nitrogen (not AB pattern), and three CF_2s at 124-127 ppm (not AB pattern). From the chemical shifts of CF_3s, one is a terminal CF_3, and the other a branched CF_3. While there was found no AB pattern on the CF_2s of a pyrrolidine and piperidine ring with no CF_3 substituent (of 5 and 13), the involvement of a CF_3 group in the ring afforded the rigidity to the pyrrolidine ring which was demonstrated by the AB patterns of the three

CF_2s of the ring. Therefore, the branched CF_3 was located at the next carbon but one to the nitrogen of the F-pyrrolidine ring, being consistent with the CF's chemical shift of 184.6 ppm (much lower if located next to nitrogen).

The highest mass (m/z 495) observed in the mass spectra of 14 and 15, which seemed to be a molecular ion, supported the bicyclic structures of 14 and 15. The structures of 14 and 15 were determined by their ^{19}F-NMR spectra shown in Table IV.

Fluorination of 4 gave a very mixture consisting of at least 10 components including minor ones. Six major components 16 to 21 were isolated by preparative g.l.c. (column F) and their ^{19}F-NMR were measured. The structures shown in Table V were assigned by analogy.

All the compounds listed in Table I was numbered in elution order on the g.l.c. column. As is evident from the structures listed in Table I, the elution order has rules relating to the structure, and gives useful structural information on these kinds of F-congeners.

1. F-monocyclic < F-bicyclic
2. 5-membered ring < 6-membered ring
3. straight chain < branched chain

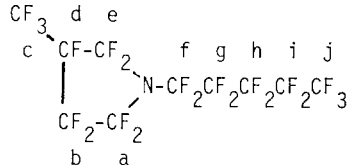
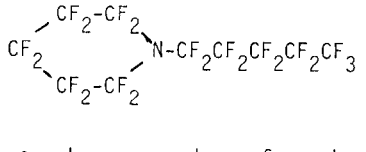
The results of the electrochemical fluorination of 1 to 4 were featured by the following observations.

1. Ring opening reactions occur only at cycloalkane rings (if the nitrogen fluorides which were omitted from our research work are not considered).
2. Bond scission predominantly occurred at a tertiary carbon.
3. All the products were explanable by (A) a ring contraction reaction, (B) a ring opening reaction at a tertiary carbon atom (in some cases followed by the isomerization from a straight chain to a branched one) and their combination.
4. Ring-contracted products arise from 6-membered rings but not 5-membered ones (5-membered rings are therefore recommended to avoid ring-contracted by-products).

The predominant factor which appears to operate in these processes is steric hindrance. The ring opening reaction occurs at more strained bonds such as bonds of F-cycloalkane rings involving tertiary carbon. As is mentioned before, it is spectroscopically supported that F-cycloalkanes are more strained than F-heterocycles. The product structures formed in the electrochemical fluorination of 4 are illustrated in Fig. 2.

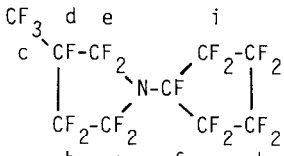
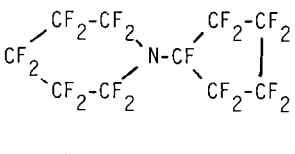
TABLE IV

^{19}F-NMR spectra of products 12, 13, 14, and 15 obtained by fluorination of 3.

Compound		Chemical shift		$J(Hz)^1$
12		a	83.5(1F)	J_{AB} = 184
			91.4(1F)	
		b	125.7(1F)	J_{AB} = 294
			131.4(1F)	
		c	74.3	
		d	184.6	
		e	81.6(1F)	J_{AB} = 191
			91.4(1F)	
		f	82.5	
		g,h	124.0(4F)	
		i	127.4	
		j	82.4	
13		a	133.4	
		b	132.7(4F)	
		c	92.0(4F)	
		d	90.2	
		e,f	124.0(4F)	
		g	127.3	
		h	82.3	

(Continued)

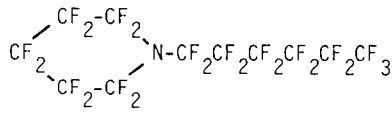
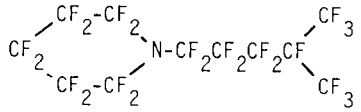
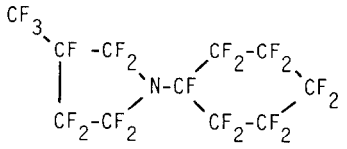
TABLE IV (cont.)

Compound		Chemical shift		$J(Hz)^1$
14		a	83.2(1F)	J_{AB} = 169
			96.7(1F)	
		b	124.1(1F)	J_{AB} = 251
			129.4(1F)	
		c	73.3	
		d	183.8	
		e	80.0(1F)	J_{AB} = 182
			90.2(1F)	
		f	139.3	
		g	115.9(1F)	J_{AB} = 260
			129.4(1F)	
		h	124.5(2F)	J_{AB} = 248
			131.6(2F)	
		i	116.5(1F)	
			134.7(1F)	J_{AB} = 261
15		a	136.2	
		b	133.4(4F)	
		c	92.0(4F)	
		d	138.0	d-e =8.0,11.3
		e	118.2(2F)	J_{AB} = 260
			131.7(2F)	
		f	128.3(2F)	
			133.8(2F)	J_{AB} = 248

[1] Values in ppm relative to internal $CFCl_3$. Only apparent chemical shifts and coupling constants were given. Relative peak intensities were correct.

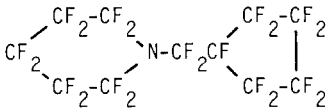
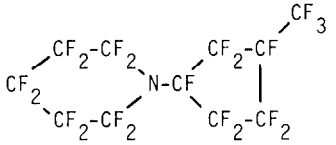
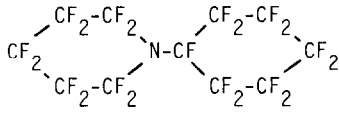
TABLE V

^{19}F-NMR spectra of products 16, 17, 18, 19, 20, and 21

Compound		Chemical shift[1]	J(Hz)
16	 a b c d e f g h i	a 135.3 b 132.7(4F) c 91.8(4F) d 90.0 e 123.2 f,g 123.6(4F) h 127.1 i 82.2	
17	 a b c d e f g h	a ca. 135 b 132.7(4F) c 91.8(4F) d 90.0 e 123.0 f 116.0 g 185.5 h 73.3(6F)	
18	 c d e b a f g h i	a 80.9(1F) 92.8(1F) b 125.6(1F) 133.3(1F) c 73.6 d 182.6 e 78.0(1F) 86.2(1F) f 160.5 g 120.5(2F) 139.0(2F) h 122.7(2F) 133.3(2F) i 124.2(1F) 142.5(1F)	J_{AB} = 187 J_{AB} = 356 J_{AB} = 187 J_{AB} = 281 J_{AB} = 319 J_{AB} = 281

(Continued)

TABLE V (cont.)

19	 a b c d e f g	a	135.5
		b	132.9
		c	92.5
		d	82.9
		e	186.0
		f	124.7(2F) J_{AB} = 290
			132.0(2F)
		g	125.5(2F) J_{AB} = 290
			134.0(2F)
20	 a b c d i h	a	135.0
		b	132.1(4F)
		c	91.8(4F)
		d	138.0
		e	109.3(1F) J_{AB} = 280
			133.0(1F)
		f	184.6
		g	74.4
		h	124.7(1F) J_{AB} = 280
			135.0(1F)
		i	119.9(1F) J_{AB} = 280
			135.0(1F)
21	 a b c d e f g	a	135.7
		b	130.8(4F)
		c	86.7(4F)
		d	154.9
		e	118.5(4F) J_{AB} = 300
			138.6(4F)
		f	122.3(4F) J_{AB} = 300
			133.2(4F)
		g	123.6(1F) J_{AB} = 300
			142.5(1F)

1 Values in ppm relative to internal $CFCl_3$. Relative peak intensities were correct.

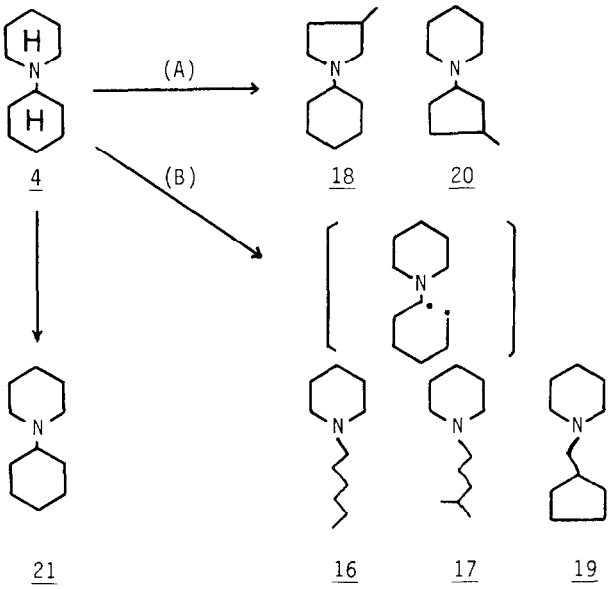


Fig. 2. Pathways for the product structures formed in the electrochemical fluorination of 4.

EXPERIMENTAL

Reagents

Bicyclic tert-amines (1-4) were prepared by the reduction of the corresponding enamines, which were derived from cyclic alkanones and sec-cyclic amines, under the conditions described elsewhere [13]. For example, a mixture of cyclopentanone (294 g), pyrrolidine (335.5 g) and benzene (300 ml) was placed in a 2-l. flask equipped with a Barrett type distilling trap and heated to reflux for 8 hr. Distillation of the reaction mixture gave N-cyclopentenyl pyrrolidine (410 g), b.p. 107-112°C/26 mmHg. To the stirred enamine (410 g) was added dropwise 146.6 ml of formic acid at 40°C at a rate such that reaction temperature did not exceed 100°C. The entire mixture was heated to 100-120°C for 2hr and made alkaline with an aqueous sodium hydroxide solution under cooling to give an oil, which was subsequently extracted with ether. The combined ethereal extract was distilled under reduced pressure to give 353 g of N-cyclopentylpyrrolidine (1), b.p. 86.5-89°C/25 mmHg, spectral data of which were consistent with those reported [13]. Compounds 2, 3, and 4 were obtained by a similar way:

2, b.p.106-109°C/26 mmHg, 86% yield; 3, b.p. 105-107°C/27 mmHg, 91% yield; 4, b.p. 104-107°C/14 mmHg, 75% yield. Anhydrous hydrogen fluoride used for electrochemical fluorination (Morita Kagaku Kogyo co., Ltd.) was more than 99.5% pure.

Apparatus

The electrochemical fluorination was carried out by the usual way as described elsewhere [5] using 1.5-l. electrolytic cell fitted with reflux condenser on the top of the cell. The effective anodic surface area was 10.5 dm^2.

Analytical gas chromatography work was done with a Shimadzu R1A gas chromatograph using columns A-C. For preparative-scale work a Shimadzu GC-4BIT gas chromatograph equipped with a thermal conductivity detector was used employing columns D-F. Nitrogen was used as a carrier gas in all cases.

For Analysis

A: a glass column (3 mm i.d. X 6 m) packed with 5% SE-30 on Chromosorb W (60-80 mesh, AW-DMCS)

B: a glass column (3 mm i.d. X 3 m) packed with 30% SE-30 on Chromosorb P (60-80 mesh, AW-DMCS)

C: a glass column (3 m i.d. X 4 m) packed with 30% SE-30 on Diasolid L-1

For Collection

D: a copper column (10 mm i.d. X 14 m) packed with 15% SE-30 on Diasolid L-1.

E: a copper column (6 mm i.d. X 3 m) packed with 30% SE-30 on Chromosorb P (60-80 mesh, AW-DMCS)

F: a copper column (10 mm i.d. X 9 m) packed with 30% SE-30 on Diasolid L-1.

NMR spectra were measured on a Hitachi R-24 high resolution spectrometer operating at 56.4 MHz, or on a Varian EM-390 instrument operating at 84.6 MHz, using $CFCl_3$ and CCl_4 as an internal standard and a solvent, respectively. Mass spectra were measured on a Shimadzu 9000 LKB at 70 eV.

Electrochemical Fluorination

Throughout the experiments no conductivity additive was used and the reaction conditions of the electrochemical fluorinations were not studied in detail.

Fluorination of 1

Starting material 1 (130 g) was fluorinated under conditions of current density 0.2-2.1 A/dm^2, cell temperature 7-12°C , 5.4-6.2 V over 79-87 hr, to give a crude product (287-342 g), which was subsequently treated with a mixture of 8N aq. NaOH and diisobutylamine (1:1 by volume) and then with a 3% KI-acetone solution. The reaction mixture thus obtained was shown by g.l.c. to contain mainly two components (over 98.9%), which were identified as N-(F-n-pentyl)F-pyrrolidine (5) (nc), b.p. 131-132 C, MS: mass number (formula, relative intensity with more than 5% except for M and M-F) m/z 464 (M-F, 32.8), 269(C_5F_{11}, 10.3), 264($C_5F_{10}N$, 100), 214(C_4F_8N, 19.7), 181(C_4F_7, 7.2), 176(C_4F_6N, 9.8), 164(C_3F_6N, 6.7), 150(C_3F_6, 6.1), 131(C_3F_5, 14.4), 119(C_2F_5, 25.6), 114(C_2F_4N, 14.4), 100(C_2F_4, 20.0), 69(CF_3, 77.0), and N-(F-cyclopentyl)-F-pyrrolidine (6) (nc), b.p. 130-130.5°C MS: m/z 445(M, 1.0), 426($C_9F_{16}N$, 37.2), 326($C_7F_{12}N$, 15.9), 295($C_6F_{11}N$, 25.0), 264($C_5F_{10}N$, 10.6), 181(C_4F_7, 7.9), 176(C_4F_6N, 11.4), 169(C_3F_7, 14.9), 150(C_3F_6, 5.0), 131(C_3F_5, 100), 100(C_2F_4, 22.4), 69(CF_3, 25.6). The yield of a mixture of 5 and 6 was 55% (two runs).

Fluorination of 2

Fluorination of 2 (130 g) with cell temperature of 4-12 C , voltage of 5.0-6.0 V, an anodic current density of 0.4-1.9 A/dm^2 gave 86.5-181.3 g of fluorinated products. The crude product was treated chemically as before and then distilled at 196 mmHg to give a bulk fraction (bp 95-105.5°, 52-101 g) which contained, by g.l.c., five components. Preparative g.l.c. (performed twice to obtain pure samples using the column D at an isothermal temperature of 50 C) gave N-(F-n-hexyl)-F-pyrrolidine (7) (nc), 9.6% (by g.l.c.) MS: m/z 514(M-F, 22.7), 264($C_5F_{10}N$, 100), 231(C_5F_9, 5.2), 214(C_4F_8N, 15.6), 176(C_4F_6N, 7.8), 169(C_3F_7, 11.7), 164(C_3F_6N, 5.2), 150(C_3F_6, 5.2), 131(C_3F_5, 14.3), 119(C_2F_5, 19.5), 114(C_2F_4N, 11.7), 100(C_2F_4, 13.0), 69(CF_3, 61.7), an unseparable mixture of N-(F-3-methylpentyl)-F-pyrrolidine (8a) (nc) and N-(F-isohexyl)-F-pyrrolidine (8b) (nc) in the ratio of 3 to 8 (by ^{19}F- NMR), 6.9% (by g.l.c.), MS: m/z 514(M-F, 34.6), 319(C_6F_{13}, 7.7), 281(C_6F_{11}, 9.0), 264($C_5F_{10}N$, 100), 231(C_5F_9, 7.7), 214(C_4F_8N, 15.4), 181(C_4F_7, 7.7), 176(C_4F_6N, 10.3), 169(C_3F_7, 10.3), 164(C_3F_6N, 5.1), 150(C_3F_6, 5.1), 131(C_3F_5 17.9), 119(C_2F_5, 21.8), 114(C_2F_4N, 12.8), 100(C_2F_4, 20.5), 69(CF_3, 89.7), N-(F-cyclopentylmethyl)-

F-pyrrolidine (9) (nc), 1.5% (by g.l.c.) MS: m/z 476(M-F, 21.4), 281(C_6F_{11}, 33.9), 264($C_5F_{10}N$, 100), 231(C_5F_9, 12.5), 214(C_4F_8N, 14.3), 181(C_4F_7,14.3), 176(C_4F_6N, 7.1), 164(C_3F_6N, 7.1), 150(C_3F_6, 8.9), 131(C_3F_5, 28.6), 119(C_2F_5, 8.9), 114(C_2F_4N, 10.7), 100(C_2F_4 17.9), 93(C_3F_3, 7.1), 69(CF_3,60.7), N-(F-methylcyclopentyl)-F-pyrrolidine (10) (nc), 24.7% (by g.l.c.), MS: m/z 476(M-F, 48.5), 326($C_7F_{12}N$, 27.9), 295($C_6F_{11}N$, 25.0), 281(C_6F_{11}, 5.9), 264($C_5F_{10}N$, 12.5), 181(C_4F_7, 100), 176(C_4F_6N, 12.5), 169(C_3F_7, 13.2), 150(C_3F_6, 9.6), 145(C_3F_5N, 5.1), 131(C_3F_5, 35.3), 119(C_2F_5, 5.9), 100(C_2F_4, 24.3), 69(CF_3, 32.4) and N-(F-cyclohexyl)-F-pyrrolidine) (11) (nc), 56.5% (by g.l.c.), MS: m/z 495 (M^+, 3.0), 476(M-F, 30.7), 326($C_7F_{12}N$, 12.5), 295($C_6F_{11}N$, 8.8), 264($C_5F_{10}N$, 8.7), 231(C_5F_9, 5.1), 181(C_4F_7, 11.6), 176(C_4F_6N, 11.3), 169(C_3F_7, 7.8), 131(C_3F_5, 100), 100(C_2F_4, 16.1), 69(CF_3, 28.7), b.p. of 11 (purity 70% by g.l.c.), 147-148°C.

Fluorination of 3

Compound 3 (130 g) was fluorinated under the conditions of 5.2-6.4 V, 10-20°C, 2-20 A/dm^2 to give 326.1 g of fluorinated products. The product weight decreased to 215.3 g after being treated with an alkali-amine mixture and KI-acetone as before. The product thus obtained was analyzed by g.l.c. using the column B to give 4 major peaks 12, 13, 14 and 15 at 13.6, 15.8, 20.5, and 25.4 min. with percentages against the total peak area of 6.0, 19.1, 21.3 and 45.3%, respectively. These components were isolated by preparative-scale g.l.c. using the column D and examined spectroscopically. Assigned compounds were N-(F-n-pentyl)-3-(F-methyl)-F-pyrrolidine (12)(nc), MS: m/z 514(M-F, 29.2), 314($C_6F_{12}N$, 96.4), 269(C_5F_{11}, 16.1), 226(C_5F_8N, 5.8), 181(C_4F_7, 16.1), 164(C_3F_6N, 16.1), 131(C_3F_5, 26.3), 119(C_2F_5,27.7), 114(C_2F_2N, 32.1), 100(C_2F_4, 11.7), 69(CF_3, 100), N-(F-n-pentyl)-F-piperidine (13) (nc), MS: m/z 514(M-F, 22.7), 314($C_6F_{12}N$, 100); 269(C_5F_{11}, 18.0), 264($C_5F_{10}N$, 140), 226(C_5F_8N, 6.7), 181(C_4F_7, 12.0), 176(C_4F_6N, 6.7), 169(C_3F_7, 8.0), 131(C_3F_5, 22.7), 119(C_2F_5, 37.3), 114(C_2F_2N, 14.0), 100(C_2F_4, 28.7), 69(CF_3, 86.7); N-(F-cyclopentyl)-3-(F-methyl)-F-pyrrolidine (14)(nc), bp. 149-150°, MS; m/z 495(M, 0.8), 476(M-F, 36.5), 376($C_8F_{14}N$, 10.3), 345($C_7F_{13}N$, 20.6), 314($C_4F_{12}N$, 8.3), 219(C_4F_9, 5.6), 181(C_4F_7, 15.1), 176(C_4F_6N, 9.6), 131(C_3F_5, 100), 100(C_2F_4, 11.9), 69(CF_3, 27.0); N-(F-cyclopentyl)-F-piperidine (15)(nc), bp 106-107 C/198 mmHg, MS: m/z 495(M, 0.7), 476(M-F, 30.3), 376($C_8F_{14}N$, 25.7), 345($C_7F_{13}N$, 6.3), 326

($C_7F_{12}N$, 5.3), 314($C_6F_{12}N$, 6.3), 181(C_4F_7, 11.8), 176(C_4F_6N, 11.8), 131(C_3F_5, 100), 119(C_2F_5, 6.6), 100(C_2F_4, 36.8), 69(CF_3, 34.2).

Fluorination of 4

Electrochemical fluorination of 4 (579 g, 3.5 mol) was conducted under the conditions of 5.8-6.4 V, 3-8°C, 0.4-2.0 A/dm^2 over 340 hr (electricity passed: 4338 Ahr) to give 1405 g of the fluorinated liquid products. The product weight decreased to 958 g (52%) after being treated with an alkali-amine mixture and a 3% KI-acetone solution as before. Five major components were separated by preparative-scale gas chromatography using the column E and identified by ^{19}F-NMR and MS: N-(F-hexyl)-F-piperidine (16) (nc); (15.7%) MS: m/z 564 (M-F, 18.9), 319(C_6F_{13}, 6.7), 314 ($C_6F_{12}N$, 100), 264($C_5F_{10}N$, 11.3), 231(C_5F_9, 7.3), 226 (C_5F_8N, 5.3), 181(C_4F_7, 6.0), 176(C_4F_6N, 6.1), 169(C_3F_7, 15.3), 131(C_3F_5, 24.0), 119(C_2F_5, 32.0), 100(C_2F_4, 24.0), 69(CF_3, 66.7), N-(F-cyclohexyl)-(F-3-methyl)-F-pyrrolidine (18) (nc) : (15.0%), MS: m/z 526(M-F, 55.8), 476($C_{10}F_{18}N$, 11.3), 376($C_8F_{14}N$, 19.0), 345($C_7F_{13}N$, 21.5), 314($C_6F_{12}N$, 12.3), 281(C_6F_{11}, 5.7), 231(C_5F_9, 6.6), 219(C_2F_5, 6.1), 181(C_4F_7, 100), 176(C_4F_6N, 11.0), 150(C_3F_6, 5.7), 131(C_3F_5, 46.0), 119(C_2F_5, 7.7), 100(C_2F_4, 13.8), 69(CF_3, 39.9), N-(F-cyclopentylmethyl)-F-piperidine (19) (nc); MS: m/z 545(M, 0.8), 526(M-F, 24.4), 345($C_7F_{13}N$, 5.0), 314($C_6F_{12}N$, 100), 281(C_6F_{11}, 44.0), 264($C_5F_{12}N$, 8.8), 231(C_5F_9, 21.6), 226(C_5F_8N, 6.8), 193(C_5F_7, 7.2), 181(C_4F_7, 42.4), 176(C_4F_6N, 9.0), 131(C_3F_5, 55.2), 119(C_2F_5, 17.6), 114(C_2F_4N, 12.4), 100(C_2F_4, 30.0), 93(C_3F_3, 5.8), 69(CF_3, 74.0),
N-(F-methylcyclopentyl)-F-piperidine (20) (nc); MS: m/z 545(M, 0.7), 526(M-F, 63.6), 376($C_8F_{14}N$, 63.6), 345($C_7F_{13}N$, 15.4), 326($C_7F_{121}N$, 10.0), 314($C_6F_{121}N$, 11.8), 276($C_6F_{10}N$, 5.7), 231(C_5F_9, 6.4), 226(C_5F_8N, 6.4), 181(C_4F_7, 100), 176(C_4F_6N, 21.4), 169(C_3F_7, 5.7), 150(C_3F_6, 6.4), 145(C_3F_5N, 5.0), 131(C_3F_5, 85.7), 119(C_2F_5, 16.8), 100(C_2F_4, 60.7), 93(C_3F_3, 5.4), 69(CF_3, 71.4), N-(F-cyclohexyl)-F-piperidine (21) (nc); MS: m/z 545(M, 0.9), 526(M-F, 31.9), 376($C_8F_{14}N$, 24.7), 345($C_7F_{13}N$, 8.7), 326($C_7F_{12}N$, 5.6), 314($C_6F_{12}N$, 10.3), 281(C_8F_{11}, 5.4), 231(C_5F_9, 8.6), 226(C_5F_8N, 5.9), 181(C_4F_7, 28.9), 176(C_4F_6N, 17.4), 131(C_3F_5, 100), 119(C_2F_5, 8.7), 100(C_2F_4, 42.1), 42.1), 69(CF_3, 44.3), ^{19}F-NMR data for major products are summarized in Table V. The compound (16) collected by preparative-scale gas chromatography was contaminated by a shoulder peak component of N-(F-isohexyl)-F-piperidine (17), for which ^{19}F-NMR data is

included in Table V. Other minor components were not identified completely, but mass spectral and gas chromatographic data suggested the structures of N-(F-n-hexyl)-(F-methyl)-F-pyrrolidine (2.8%) and N-(F-methylpentyl)-(F-methyl)-F-pyrrolidine (4.9%). The yields were all calculated from the peak areas.

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