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SYNTHESIS OF PERFLUOROCHEMICALS FOR USE AS BLOOD SUBSTITUTES. PART III. [1] ELECTROCHEMICAL FLUORINATION OF QUINOLIZIDINE, 4-METHYLQUINOLIZIDINES AND 4-TRIFLUOROMETHYLQUINOLIZIDINES [2]

YOSHIHISA INOUE, YOSHIO ARAKAWA, YOUICHIRO NAITO, TAIZO ONO, CHIKARA FUKAYA KOUICHI YAMANOUCHI * and KAZUMASA YOKOYAMA

Central Research Laboratory, Green Cross Corporation, 2-1180-1, Shodai-Ohtani, Hirakata, Osaka 573 (Japan)

SUMMARY

Electrochemical fluorination of quinolizidine gave F-quinolizidine in 16-23% isolated yields. 4-Methylquinolizidine was also fluorinated electrochemically to give the corresponding amine stereoisomers along with their fragmented and rearranged products in isolated yields of 28-34% and 2-3%, respectively. Introduction of an F-methyl group into the quinolizidine in place of the methyl group prior to electrochemical fluorination did not stabilize the 4-methyl quinolizidine structure and rather allowed the formation of F-quinolizidine to a greater extent. Oxidation of 4-(F-methyl)-F-quinolizidine with fuming sulfuric acid in the presence of a catalytic amount of $HgSO_4$ gave 6-oxo-4-(F-methyl)-F-quinolizidine in 60% yield, the F-nmr spectra of which gave further support to the structure of the starting material. The physical and spectral properties of these F-chemicals are described.

INTRODUCTION

As a part of our studies on F-chemical (PFC) oxygen-transport emulsion [3], we carried out electrochemical fluorinations of N-methyldecahydroquinoline and its isoquinoline analogs [4], and found that these perfluorinated compounds exhibit favorable properties as oxygen-carrying agents in terms of both the emulsifiability and the pharmacodynamical properties [5]. We have since become interested in bicyclic F-alkanes with fused six-membered rings which incorporate a bridge-head nitrogen atom.

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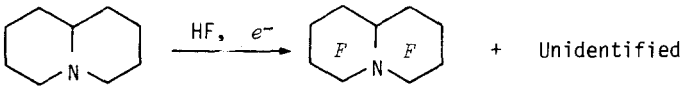
The only preceding example of such azabicyclo F-alkanes has been 1-azabicyclo[5.3.0]-F-decane which was prepared from the fluorination of quinoline by cesium tetrafluorocobaltate [6,7] a ring rearrangement being involved. There have been no reports on the electrochemical fluorinations of 1-azabicycloalkanes.

In this paper, we wish to report the first example of the synthesis of F-quinolizidine and 4-(F-methyl)-F-quinolizidine by electrochemical fluorination.

RESULTS AND DISCUSSION

Trans-quinolizidine (1), which was obtained from 2-vinylpyridine in a four-step process according to the known method, was electrochemically fluorinated to give a complex mixture containing *trans*-F-quinolizidine (2) (nc) as the major product (Scheme 1). To remove by-products containing residual hydrogen or unsaturation or nitrogen fluorides, (since such compounds are desired to be as low as possible in PFC's for use as oxygen carrying agents [3]), the mixture was treated with a mixture of an aqueous potassium hydroxide solution and diisobutylamine, subsequently with an aqueous potassium iodide-acetone solution. Subsequent isolation gave 2 in 16-23% yields.



1 2

Scheme 1.

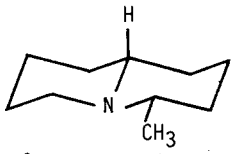
Because our interests are only in PFC's having the boiling point range of 110-165°C*, low (or high) molecular weight products outside this range were not investigated. In our product mixtures thus treated, isolable quantities of by-products were not present even though work-up procedures were carefully carried out. Product 2 was shown by g.c. with SE-30 capillary column (see EXPERIMENTAL) to be a single component (99.9% based on peak area).

* The substrates for use as oxygen carriers are required to possess an appropriate b.p. and vapor pressure (10-20 mmHg at 37°) [3].

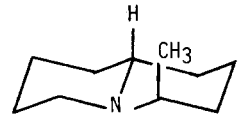
The structure of the product followed from high resolution mass spectra, IR and F-nmr. The mass spectrum of 2 gave M^+ of m/z 445 ($C_9F_{17}N$) and characteristic fragmentation patterns as observed in bicyclic PFC systems [4], suggesting at first the F-quinolizidine structure. In the F-nmr spectrum of 2, chemical shifts of the fluorine atoms of the ring seem quite likely to accord with the shifts for *trans*-F-decalin [8, 9], except for shifts of >NCF and $>NCF_2$ moved by about 30-50 ppm towards the downfield as exemplified by N-(F-methyl)-F-decahydroquinoline analogs [4]. Thus, the F-nmr spectrum of 2 showed a tertiary fluorine (>CFN<) at 132.9 ppm, AB CF_2's between 119 and 140 ppm and an AB NCF_2 between 82 and 98 ppm, proving product 2 was the *trans* form. As to F-nmr characteristics for 2, one might propose that the bridge-head nitrogen of 2 would produce a less sterically crowded environment around the nitrogen, compared with the analogous situation for the bridge-head CF in the *trans*-F-decalin system, resulting in smaller coupling constants of the $>N-CF_2-$ (in our hands, 175 Hz) than for the corresponding CF_2 of F-decalin (276 Hz), as has been seen for 1-azabicyclo[5.3.0]-F-decane (178-220 Hz)[6].

In IR analysis, only one weak band at 848 cm^{-1} is also diagnostic of the *trans* form for which bands are absent from, or very weak in, the region between 800-900 cm^{-1} [4, 10].

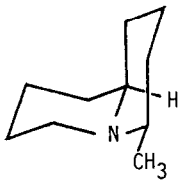
4-Methylquinolizidines, consisting of the conveniently named *trans*, *trans*-4-methylquinolizidine (3a) and its stereoisomers (3b-d) in a ratio of 72:28, were obtained by hydrogenation of 1-(2-pyridyl)pentan-4-one using 5% Rh-C as a catalyst (Scheme 2).



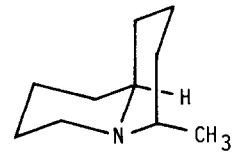
3a: *trans, trans*



3b: *trans, cis*



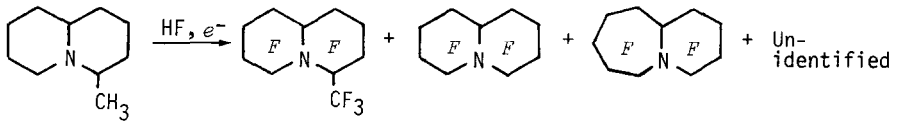
3c: *cis, trans*



3d: *cis, cis*

Scheme 2.

The stereoisomer mixture was electrochemically fluorinated without further purification considering the difficulty of the purification and the unexpected isomerization through a vigorous electrochemical fluorination process. The product thus obtained (after the alkaline-treatment) consisted of the *trans*- and *cis*-isomers of 4-(F-methyl)-F-quinolizidine (4) as the major product. The product present in second largest amount was *trans*-F-quinolizidine (2), and a new 1-azabicyclo[5.4.0]-F-undecane (5) (nc) was found in a small amount (Scheme 3).



3a-d 4 (58) 2 (5) 5 (2) (35)

Figures in parentheses indicate the product distribution in percentage.

Scheme 3.

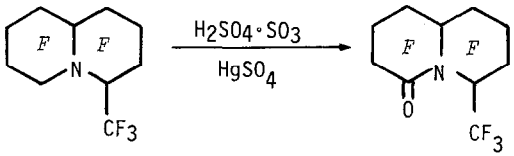
Although product 4 was shown by SE-30 capillary column to consist of two components (total 98% based on peak area) in a ratio of (typically) 71:29, it was proved to have molecular formula of $C_{10}F_{19}N$ by elemental analysis and high-resolution mass spectra. An F-nmr spectra of 4 (as the mixture) suggested that the predominant component had the structure *trans*, *trans*-4-(F-methyl)-F-quinolizidine (nc): there were present a strong signal at 72.9 ppm (CF_3), an AB CF_2 at 75.0 and 102.9 ppm ($-CF_2N<$, J=175 Hz), two CFs at 128.4 and 129.6 ppm and unassigned AB CF_2s between 113.7-146.8 ppm corresponding to 12 Fs. There was nothing at higher field beyond 146.8 ppm. The stereochemistry of the predominant component of 4 was tentatively assigned as a *trans* form based on IR analysis: the IR spectrum of 4 showed only three weak bands at 838, 880 and 898 cm^{-1} in the region of 800-900 cm^{-1}.

It was assumed that one of the other stereoisomers of 4, presumably a *cis* form, was present in fair quantity, but attempted isolation of it in pure form was proved unsuccessful, since its boiling point and g.c. behaviors were nearly the same as for the *trans* form of 4. The second stereoisomer gave an F-nmr spectrum for which an unequivocal allocation of structure is not possible at the present time.

By-product 5 , which was shown by SE-30 capillary column to be a single component, was found both intuitively and in fact not to have a ring-opened skeleton or an indolizidine-type skeleton. The mass spectrum of 5 showed M^+ or m/z 495 fitting the $C_{10}F_{19}N$ structure. No CF_3 peaks were observed in the F-nmr. Two AB CF_2's at low field (75.6-98.0 ppm) were also of use in the structure assignments of 5, being indicative of CF_2 adjacent to nitrogen. Five other AB CF_2's, a tertiary >NCF< at 124.0 ppm and unassigned signals at around 126 ppm corresponding to 4 F's were found. This signal pattern was similar to that of 1-azabicyclo[5.3.0]-F-decane [6], suggesting that product 5 had the 7-6 fused ring system. Ring expansion of N-(ω-chloroethyl)-2-pipecoline to hexamethyleneimine during electrochemical fluorination is now known [11]. A similar rearrangement of quinoline to the 7-5 fused ring system in the fluorinations with metal fluoride [6] has been already reported. The mass spectrum of 5 gave further support to the proposed structure: there are the base peak at m/z 131 and largest peaks at m/z 69 ($M-C_9F_{16}N$, 57.1% of base peak) and m/z 100 ($M-C_8F_{15}N$, 50.1%) and a quite similar pattern to 1-azabicyclo[5.3.0]-F-decane [6] was found.

The major by-product was *trans*-F-quinolizidine which was identical with the major product obtained from the fluorination of 1.

In order to confirm the proposed structure of 4, oxidation of it was conducted. Thus, compound 4 was reacted with fuming sulfuric acid in the presence of a catalytic amount of $HgSO_4$ to give 6-oxo-4-(F-methyl)-F-quinolizidine (6) (nc) in 60% yield, which was easily decomposed when exposed to moisture (Scheme 4).

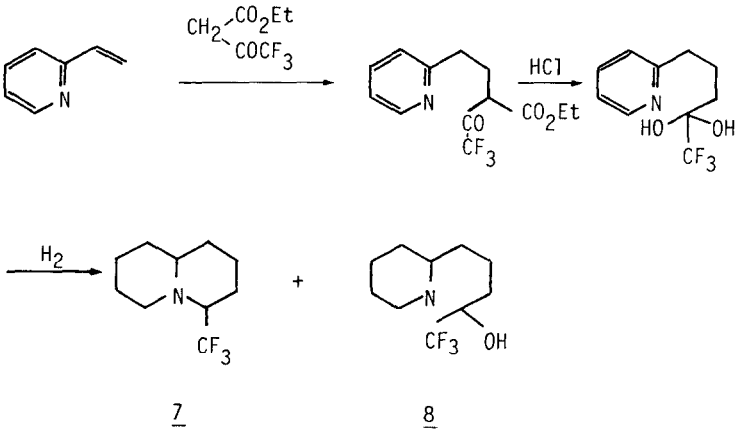


4 6

Scheme 4.

By analogy to an exemplification in the patent work of Pavlik [12] that N-(F-ethyl)-F-morpholine was sulfated by sulfur trioxide and hydrolyzed to produce 3-oxo-N-(F-ethyl)-F-morpholine, the proposed structure (6) was expected to be a product of this reaction. The structure was shown unequivocally by F-nmr: the absence of AB CF_2s at low field (<100 ppm), a strong signal at 69.0 (CF_3), four AB CF_2s at positions 1, 2, 3, 7 between 107.3 and 147.7 ppm, and a large unsplit signal for two CF_2 s and two CF s at 126.0 were clearly observed. The largest coupling constant (324 Hz) among AB CF_2s may be attributed to the geminal fluorines of CF_2 adjacent to the oxo group. The stereochemistry of product 6 cannot distinctively be allocated by nmr spectroscopy, but it seems probable that the *trans* form of the substrate could survive in the oxidation reaction. The IR spectrum of 6 clearly showed a strong band at 1770 cm^{-1} due to the amide group. The mass spectrum of 6 showed m/z 404 (M-CF_3), 323 ($C_7F_{11}NO$), 109 (C_3F_3O) and 100 (C_2F_4, base peak) giving further support to the proposed structure.

In the hope of increasing the yield of 4, 4-(F-methyl)quinolizidines (nc) were prepared and fluorinated in a similar manner, since the introduction of the F-methyl group into organic molecules to be fluorinated often gives better yields of the desired structure, as reported elsewhere [13].



7 8

Scheme 5.

Substrate 7 was prepared by the reaction of 2-vinylpyridine with trifluoroacetoacetic ethyl ester, *via* 3-ethoxycarbonyl-1,1,1-trifluoro-5-(2-pyridyl) pentan-2-one and then 1,1,1-trifluoro-2,2-dihydroxy-5-(2-pyridyl) pentane, in the overall yield of 36% (based on vinylpyridine). Substrate 7 consisted of 4 stereoisomers, of similar stereochemistry to 3a-d: the structures being *trans, trans*-4-(F-methyl)quinolizidine (7a), *trans, cis* - (7b), *cis, trans*- (7c) and *cis, cis*- (7d) with a ratio of 20:6:13:17. A by-product identified was 1,1,1-trifluoro-5-(2-pyridyl)-pentan-2-ol (8) (nc) (Scheme 5).

Substrate (7) (as the stereoisomer mixture) was electrochemically fluorinated using conditions similar to those for the unfluorinated analogs (3) to give a complex mixture in a poorer weight recovery of product (141% *versus* 189%, after the work-up treatment as described in the experimental section). The product mixture was analyzed by g.c. to consist of the perfluorinated counterpart, *trans*-F-quinolizidine and unidentified material in a ratio of 35:25:40. This result quite discouraged us: in contrast to 3, substrate 7 gave lower yields of the desired product but higher yields of fragmentation products. Thus, we concluded that 4-(F-methyl)quinolizidine may not be a superior substrate to the unfluorinated one for electrochemical fluorination.

EXPERIMENTAL

Throughout this article the 'F-' symbol (also in the center of a ring) signifies all bonds are to fluorine, and the 'F' system for naming perfluorinated organic compounds is based on the authorized ACS nomenclature [14].

Spectroscopy

IR were run on a Shimadzu IR-420 spectrophotometer. ^{1}H-nmr spectra were recorded on a Hitachi R-24B instrument (60 MHz) using tetramethylsilane as an internal standard. ^{13}C-nmr spectra were obtained on a JEOL FX-900 spectrometer at the Osaka Municipal Technical Research Institute. ^{19}F-nmr spectra were recorded on a Hitachi R-24F (56.4 MHz) or Varian EM-390 spectrometer (84.6 MHz) using trichlorofluoromethane as an internal standard. Upfield shifts are quoted as positive.

Mass spectral data were obtained at an ionizing voltage of 70 eV on a Shimadzu QP-1000 or a Shimadzu-LKB GC-MS. High-resolution mass spectra were run on a Shimadzu 9020-DF with a Hitachi Data Processing System M-003 at the Shimadzu Co. Analytical Center.

Analytical g.c.s were carried out on a Shimadzu GC-6A using 20% PEG 20M + 10% KOH column (3 mm i.d., 2 m long, abbreviated as PEG column) or 5% SE-30 on Chromosorb W (3 mm i.d., 6 m long, abbreviated as SE column), and on a Shimadzu GC-9A (FID) using SE-30 capillary column (0.25 mm i.d., 100 m long, film thickness 0.4 μm) with split ratio of 1/100 at 50°. Preparative-scale g.c. was carried out with a Shimadzu GC-4B using copper column (20 mm i.d., 14 m long) packed with 30% SE-30 on Diasolid L-1.

Melting points were determined with a Yanagimoto Micro Melting-Point Apparatus. Melting points and boiling points were not corrected.

Fluorination apparatus

Fluorination was carried out in the usual way as described elsewhere [15] using an electrolytic cell of 1.5 liters capacity fitted with reflux condenser (-20°C) on the top of the cell: The effective anodic surface area was 10.2 dm^2. Conductivity additives were not used throughout the experiments.

Trans-F-quinolizidine (2)(nc)

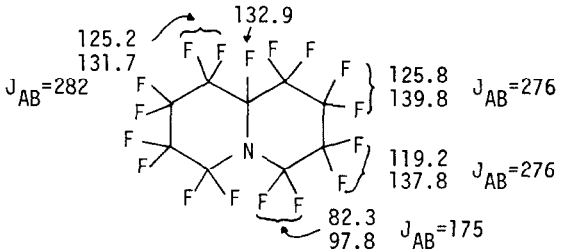
(a) Preparation of *trans*-quinolizidine (1)

According to the method of Y. Arata [16], 1 was obtained from 2-vinylpyridine in a four-step process as a colorless liquid in 32% overall yield, b.p. 79-81° (23 mmHg)(lit. 73-75° (17 mmHg)). IR (film, cm^{-1}): 2800, 2780, 2700 (Bohlmann bands for *trans* form). MS: m/z 139 (M^+), 138 (base peak).

(b) Fluorination of 1

In a typical experiment, 130 g of 1 was dissolved in about 1.2 liters anhydrous hydrogen fluoride in the cell. The electrolysis was carried out with the cell voltage of 5.2-6.0 V, at the cell temperature 7-19° for 58-78 hrs (Passed electricity: 947-1091 Ahr). The crude product (228-260 g) was washed with an aqueous sodium bicarbonate solution and mixed with a mixture of 80% potassium hydroxide solution and diisobutylamine. The mixture was refluxed for 120 hrs, then washed with water, concentrated sulfuric acid and

water in that order and subsequently treated with 3% potassium iodide aqueous acetone solution. The resultant F-chemical (140-157 g) was shown by g.c. (SE column) to be a complex mixture with one major component (typically 55% by g.c.), and separated by spinning-band column distillation into a bulk fraction boiling at 127-132° and still residue. The fraction was further fractionated by preparative-scale g.c. giving 2 identified as *trans*-F-quinolizidine (2). The isolated yield of 2 ranged from 16 to 23%. b.p. 129-130°. d_4^{18} 1.919. (Found: m/z, 444.96466; F, 72.4%. $C_9F_{17}N$ requires M, 444.9759; F, 72.6%). F-nmr ($CDCl_3$, ppm): Only assigned signals are shown below.



IR (film, cm^{-1}): 1364(s,sh), 1350(s,br), 1276(s), 1196(s,sh), 1168(s), 1154(s), 1138(m), 1180(s), 1080(s), 1054(s), 990(w), 942(s), 848(w), 796(w), 776(w), 758(w). MS (m/z, formula, more than 3% intensity of the base peak in parentheses): 445, M^+ (6.4); 426, $C_9F_{16}N$ (24.6); 376, $C_8F_{14}N$ (3.1); 226, C_5F_8N (3.4); 181, C_4F_7 (5.4); 176, C_4F_6N (3.6); 169, C_3F_7 (9.3); 133, C_3F_5 (50.0); 119, C_2F_5 (10.7); 114, C_2F_4N (4.1); 100, C_2F_4 (100), 93, C_3F_3 (3.1); 69, CF_3 (35.7).

4-(F-Methyl)-F-quinolizidine (4) (nc)

(a) Preparation of 4-methylquinolizidines (3a-d)

A solution of ethyl-β-(2-pyridyl)ethylacetoacetate (250 g) [17], b.p. 135-145° (1 mmHg), IR (film, cm^{-1}): 1730, 1710, in 20% hydrochloric acid (1.25 liters) was refluxed for 4 hrs. The reaction mixture was made alkaline with 20% sodium hydroxide solution and extracted with ether. The ethereal layer was distilled to give 1-(2-pyridyl)pentan-4-one (159 g), b.p. 94-97° (1 mmHg), IR (film, cm^{-1}): 1710, H-nmr ($CDCl_3$, ppm): 2.10 (s, 3H), which was then hydrogenated over 5% Rh-C (450 mg) at 100° under 20-25 kg/cm^2 for

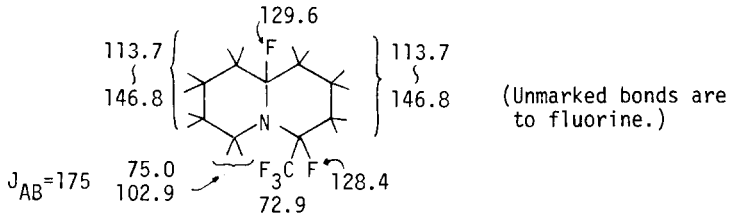
90 minutes. The catalyst used was removed by filtration and the filtrate was distilled to give an isomer mixture of 3 (23.5 g) as a colorless liquid, b.p. 83-105° (18 mmHg). The product was shown by g.c. to consist of five components in a ratio of 340(3a):10(3b):110(3c):1(3d):8(3e), which were subsequently identified as follows; a bulk fraction of b.p. 92° (25 mmHg) was chromatographed on a neutral alumina column with petroleum ether as eluent, giving *trans, trans*-4-methylquinolizidine (3a), b.p. 92-93° (26 mmHg)(lit. [18], b.p. 82° (17 mmHg)); H-nmr ($CDCl_3$, ppm): 1.07 (d, J=6, 3H), 1.0-2.2 (m, 15H), 3.2-3.4 (m, 1H); ^{13}C-nmr ($CDCl_3$): 21.1, 24.8, 25.1, 26.7, 34.4, 34.4, 35.8, 51.7, 58.6, 62.8; MS: 153(M^+), 152, 138(M-CH_3, base), 110; relative retention time (T_R): 1.0 (PEG column, 200°), and *trans, cis*-4-methylquinolizidine (3b), b.p. 93° (26 mmHg) (lit. [18], b.p. 88° (22 mmHg)); H-nmr ($CDCl_3$, ppm): 1.0 (d, J=6, 3H), 1.0-2.3 (m, 14H), 2.3-2.8 (m, 1H 3.1-3.45 (m, 1H); ^{13}C-nmr ($CDCl_3$): 9.3, 24.9, 19.1, 26.6, 32.8, 34.5, 34.6, 52.8, 53.2, 54.4, which were coincident with those reported [19]; MS of 3b was the same as that of 3a; T_R: 1.22.

A bulk fraction of b.p. of 107-108° (24 mmHg) was also chromatographed on a neutral alumina column with petroleum ether-ether (9:1) as eluent, giving *cis, trans*-4-methylquinolizidine (3c), b.p. 109° (26 mmHg); H-nmr ($CDCl_3$, ppm): 0.85 (d, J=-6, 3H), 0.8-2.4 (m, 13H), 2.4-3.3 (m, 3H); ^{13}C-nmr ($CDCl_3$): 22.4, 23.7, 24.1, 29.7, 30.4, 35.7, 38.0, 45.5, 50.3, 58.5; MS: 153(M^+), 138(M-CH_3), 110(base). T_R: 1.69. Attempted isolation of 3d and 3e, T_R's of which were 1.97 and 2.26 respectively, from the mixture of 3 was proved unsuccessful, however, each MS was the same as those of 3a-c. Although it is difficult to predict these by-product structures only from their mass spctra, we tentatively assigned 3d as one of the stereoisomers, *cis , cis* -4-methylquinolizidine and presumed 3e as a ring-opened isomer, 5-(2-piperidinyl)pent-3-ene, from T_R's data.

(b) Fluorination of 3a-d

The stereoisomer mixture of 3a-d (containing 3e as before)(130 g) was electrochemically fluorinated with a voltage of 5.6-6.2 V and a cell temperature of 4-12°.After 69 hrs(918 Ahr) electrolysis, anhydrous hydrogen fluoride was distilled with the aid of blowing helium. The remaining F-chemical (306 g) was washed with an aqueous sodium bicarbonate solution (200 ml X 2) and treated with the alkali-amine mixture and potassium iodide solution as described before giving 245 g of F-chemicals,which was shown by g.c. to consist of 4, 2, 5 and unknowns in a ratio of 58:5:2:35.

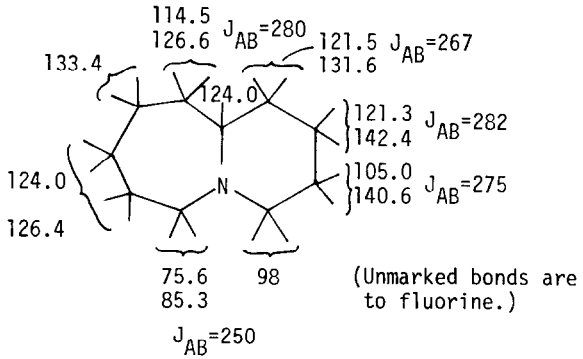
The isolated yield of 4 ranged from 28 to 34%. Preparative-scale g.c. gave 4-(F-methyl)-F-quinolizidine (4), b.p. 149-149.5°, d_4^{18} 1.972, of which analytical g.c. by SE-30 capillary column showed two components in a ratio of 71:29. (Found (as the mixture): m/z, 494.9820; F, 72.75%. $C_{10}F_{19}N$ requires M, 494.9729; F, 72.91%). F-nmr as the mixture ($CDCl_3$, ppm): Only assigned signals are shown below.



IR (film, cm^{-1}): 1348(s), 1308(s,br), 1274(s,sh), 1240(vs,br), 1200(vs,br), 1194(s,sh), 1166(s), 1152(s), 1138(s), 1110(s), 1074-60(br), 1036(s), 1000(m), 970(w), 916(s), 898(w), 880(w), 838(w), 762(m), 722(s).
MS: 495, M^+ (0.6); 476, M-F (56.2); 426, $C_9F_{16}N$ (78.7); 376, $C_8F_{14}N$ (12.4); 338, C_6F_{14} (3.4); 326, $C_7F_{12}N$ (3.9); 276, $C_6F_{10}N$ (3.4); 238, C_6F_8N (4.5); 226, C_5F_8N (7.3); 219, C_4F_9 (6.2); 181, C_4F_7 (14.6), 176, C_4F_6N (5.1); 169 (44.9); 131 (47.2); 119 (19.1); 114, C_2F_4N (3.4); 112, C_3F_3 (3.9); 100 (55.1); 93 (5.6); 69 (100). We assigned the major component of 4 as *trans*, *trans*-4-(F-methyl)-F-quinolizidine from the rationale described in the text.

Two by-products isolated by preparative-scale g.c. were identified as *trans*-F-quinolizidine (2) by comparison of its F-nmr spectrum with that obtained from 1, and as 1-azabicyclo[5.4.0]-F-undecane (5) (Found: m/z, 494.98053. $C_{10}F_{19}N$ requires M, 494.9727). These by-products were shown by SE-30 capillary column to be a single component.
IR (film, cm^{-1}): 1350(s), 1330(m), 1302(s,br), 1278(s), 1256(s,sh), 1240(s,sh), 1220-1198(vs,br), 1188(s), 1168(s), 1150(s), 1140(s), 1110(s), 1080(m), 1054(s), 1038(s), 994(s), 980(s), 916(s), 858(w), 838(w), 816(w), 768(m), 656(m), 628(w), 604(w), 502(w).
MS: 495, M^+ (1.5); 476, $C_{10}F_{19}N$ (12.2); 426, $C_9F_{16}N$ (2.7); 276, $C_6F_{10}N$ (2.7); 226, C_5F_8N (4.1); 181 (8.0); 176, C_4F_6N (5.1); 169 (8.2); 131 (100); 119 (8.4); 114, C_2F_4N (6.4); 100 (50.1); 69 (57.1).

F-nmr ($CDCl_3$, ppm): Only assigned signals are shown.



(c) Preparation of 4-(F-Methyl)quinolizidines (7a-d) (nc)

2-Vinylpyridine (231 g) was reacted with trifluoroacetoacetic ethyl ester (269.6 g) in xylene (300 ml) at reflux temperature for 6 hrs to give 3-ethoxycarbonyl-1,1,1-trifluoro-5-(2-pyridyl)pentan-2-one, pale yellow liquid, b.p. 107-110° (0.7 mmHg), IR (film, cm^{-1}) 1735, 261.7 g (61.8%), which was then heated to reflux with 20% HCl (1.3 liters) followed by aqueous 20% sodium hydroxide solution to afford 1,1,1-trifluoro-2,2-dihydroxy-5-(2-pyridyl)pentane (nc), 177.5 g (83.4%), colorless needles (acetone-petroleum ether), m.p 76-77.5° (Found: C, 51.03; H, 5.10; N, 5.82%. $C_{10}H_{12}F_3NO_3$ requires C, 51.07; H. 5.14; N, 5.96%) H-nmr (Me_2SO-d_6, ppm): 1.45-2.25 (m, 4H), 2.55-3.05 (m, 2H), 6.30-7.00 (br, 2H, exchanged with D_2O), 7.00-7.45 (m, 2H), 7.50-7.90 (m, 1H), 8.35-8.60 (m, 1H). ^{13}C-nmr (Me_2SO-d_6, ppm): 24.8, 34.5, 37.3, 92.7, (q, J=29.3 Hz), 121.1, 122.7, 124.3 (q, J=289.3 Hz), 136.4, 148.8, 161.3. F-nmr (Me_2SO-d_6, ppm): 82.9(s). IR (KBr, cm^{-1}): 3370, 1600, 1570.

The hydrate (86 g), acetic acid (430 ml) and 5% Rh-C (2.8 g) were placed in a one liter autoclave. Hydrogenations were carried out at 100-130° with 20-25 Kg/cm^2 pressure for 1 hr. The reaction mixture was filtered to remove the catalyst. The filtrate was condensed under reduced pressure on a evaporator, made alkaline with an aqueous sodium hydroxide solution, and extracted with ether. The combined ether extract was washed with water, dried over anhydrous sodium sulfate, and condensed under reduced pressure to give an oil, which separated on collection into a hexane layer and precipitates by addition of n-hexane (125 ml). Distillation of the hexane layer gave an isomer mixture of 7 as a colorless liquid, 47 g (62%), b.p. 84-110° (15 mmHg).

The product mixture was shown by g.c. (PEG column 100°) to consist of five components; 7a, 7b, 7c, 7d, and 7e in the ratio of 20:6:13:17:1. The 7a-c were subsequently identified as stereoisomers of 7 by analogy with the structure determinations for 3a-c, *trans, trans* -4-(F-methyl)-quinolizidine (7a), T_R 1.00 (Found: M^+, 207.1240. $C_{10}H_{16}F_3N$ requires M, 207.1234), F-nmr ($CDCl_3$, ppm): 67.5 (3F, d, J=7.5 Hz). MS: 207 (M^+), 206, 178, 151, 138 (base), 123, 100, 83, 55; *trans, cis*-4-(F-methyl)quinolizidine (7b), T_R 1.10 (Found: M^+, 207.1243), F-nmr ($CDCl_3$, ppm): 61.1 (3F, d, J-9.6 Hz). MS of 7b was the same as that of 7a; *cis, trans* -4-(F-methyl)quinolizidine (7c), T_R 3.23 (Found: M^+, 207.1215), F-nmr ($CDCl_3$, ppm): 68.2 (3F, d, J-8.8 Hz). MS: 207 (M^+), 178, 164 (base), 138, 82, 56. Compounds 7d and 7e gave the following spectroscopic data, respectively: T_R 3.50 and 4.82 (Found: M^+, 207.1203 and 207.1192), F-nmr ($CDCl_3$, ppm): 67.1 (3F, d, J=7.6 Hz) and 68.7 (3F, d, J=9.0 Hz). Those MS are the same as that of 7c. Their stereochemistry were not investigated further, but we tentatively assigned 7d as the remaining *cis, cis*-form of the stereoisomers and presumed 7e as the ring-opened isomer, 1,1,1-trifluoro-5-(2-piperidinyl)pent-3-ene in the same manner as described before for 3d and 3e.

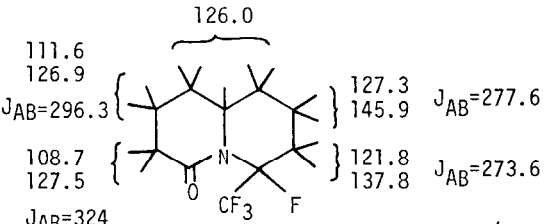
The precipitate was recrystallized from methanol-n-hexane mixture to give 1,1,1-trifluoro-5-(2-piperidyl)pentan-2-ol (8) (nc), 5 g (6%), m.p. 100.5-101.5° (Found: C, 53.12; H, 8.13; N, 6.10. $C_{10}H_{18}F_3NO$ requires C, 53.32; H, 8.05; N, 6.22). H-nmr ($CDCl_3$, ppm): 0.80-2.10 (m, 12H), 2.20-3.30 (m, 3H), 3.40-4.25 (m, 1H), 4.08 (br-s, 2H, exchanged with D_2O). F-nmr ($CDCl_3$, ppm): 77.8 (d, J=7.7 Hz). IR (KBr, cm^{-1}): 3300, 1270, 1165, 1120. MS: 225 (M^+), 224, 84 (base).

(d) Fluorination of 7a-d

Distilled 7 (stereoisomer mixture as before, 91 g (0.439 mol)) was electrochemically fluorinated with a voltage of 5.4-8.0 V and a cell temperature of 5-7°. After 68 hrs electrolysis, anhydrous hydrogen fluoride was distilled with the aid of blowing helium. The remaining F-chemical layer (160 g) was washed with an aqueous sodium carbonate solution (200 ml x 2) and treated with the alkali-amine mixture and KI-acetone solution as before, giving 128.5 g of F-chemicals, which was shown by g.c. to consist of 4, 2 and unknown products in a ratio of 35:25:40, and was subsequently identified by their mass spectra and by a comparison of their F-nmr spectra with those obtained from the fluorinations of 1 and 3.

6-Oxo-4-(F-methyl)-F-quinolizidine (6) (nc)

According to the method of Nagase [20] a stereoisomer mixture of 4 as before (mainly *trans*, *trans*-form, 71%, by g.c., 3.145 g (6.35 mmol)), 30% fuming H_2SO_4 (5.6 g) and mercury (II) sulfate (22 mg) was heated to 160-175° in a sealed tube over 42 hrs. An F-chemical layer (an upper layer) which formed upon cooling was quickly separated using a separatory funnel. The product mixture (2.3 g) was shown by g.c. to consist almost entirely of a single component and was subsequently distilled at atmospheric pressure to give 6-oxo-4-(F-methyl)-F-quinolizidine (6), 1.8 g, b.p. 138-140°, which fumed when exposed to moisture. F-nmr ($CDCl_3$, ppm):



(Unmarked bonds are to fluorine.)

IR (film, cm^{-1}): 1770 ($\nu_{C=O}$). MS: 423, $C_9F_{15}NO$ (13.0); 404, $C_9F_{14}NO$ (14.2); 376, $C_8F_{14}N$ (5.3); 354, $C_8F_{12}NO$ (3.7); 338, $C_8F_{12}N$ (3.5); 326, $C_7F_{12}N$ (4.9); 323, $C_7F_{11}NO$ (48.1); 288, $C_7F_{10}N$ (5.2); 276, $C_6F_{10}N$ (3.4); 243, C_6F_9 (3.6); 238, C_6F_8N (16.0); 228, C_5F_8O (6.2); 212, C_5F_8 (4.4); 195, C_4F_7N (4.5); 193, C_5F_7 (3.5); 188, C_3F_8 (3.1); 181, C_4F_7 (12.1); 178, C_4F_6O (3.1); 176, C_4F_6N (5.5); 173, C_4F_5NO (4.5); 169, C_3F_7 (7.7); 162, C_4F_6 (4.5); 150, C_3F_6 (69.5); 143, C_4F_5 (10.9); 138, C_2F_6 (7.1); 119, C_2F_5 (10.0); 112, C_3F_4 (23.8); 109, C_3F_3O (9.4); 100, C_2F_4 (100); 9.3, C_3F_3 (14.9); 81, C_2F_3 (3.7); 76, C_2F_4 (5.7); 69, CF_3 (58.4).

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