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NUCLEOPHILIC SUBSTITUTION REACTIONS OF THE HETEROCYCLIC FLUORO-OLEFIN PERFLUORO-(3,6-DIHYDRO-2-METHYL-2H-1,2-OXAZINE)

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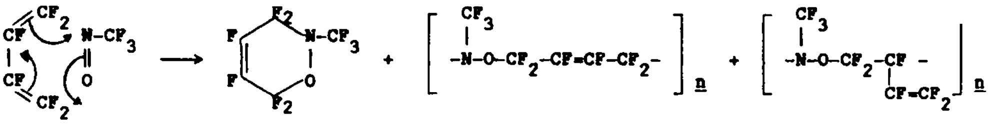
Abstract - Perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) reacts with nucleophiles to produce mixtures of the 4- and 5-substituted derivatives, with the latter in preponderance. Neither double bond isomerisation nor allylic substitution are observed. Bistrifluoromethylnitroxide adds quantitatively to the olefinic bond of the parent oxazine. Perfluoro(3,6-dihydro-2-methyl-2H-1,2-oxazine) exhibits a high thermal and photolytic stability. This, together with the failure of the oxazine to isomerise is rationalised in terms of partial aromaticity resulting from negative hyperconjugation. Possible explanations for the observed substitution pattern are advanced.

INTRODUCTION

Perfluorobutadiene and trifluoronitrosomethane react together to produce the Diels-Alder adduct, perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine), (1), plus a 1:1 alternating copolymer with internal and pendent vinyl groups (2a and 2b)[1].



(1) (2a) (2b)

Although reactions of perfluoro-olefins with nucleophiles have been extensively studied, there are few reports on the reactions of compounds where the fluoro-olefin moiety forms part of an aliphatic heterocyclic system. Here we describe an investigation of reactions of nucleophiles and free-radicals with the oxazine (1), and compare the findings with those for other polyfluoro-olefins. The results also provided an insight into the nature of nucleophilic and free-radical attack on the $-N(CF_3).O.CF_2.CF:CF.CF_2-$ grouping as background to studies on the cross-linking of nitroso rubbers[2].

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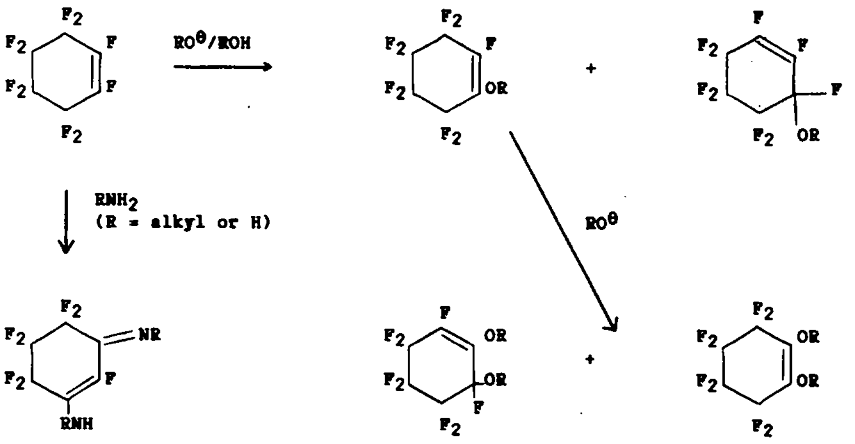
2.

Although the original work was carried out some years ago[3], a mechanistic interpretation only became possible in the light of recent advances in the theory of nucleophilic vinylic substitution[4,5], in frontier orbital approaches to nucleophilic attack on fluoro-olefins[6], and in the concept of anionic hyperconjugation[4,5,7,8].

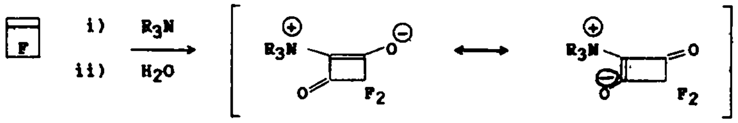
RESULTS AND DISCUSSION

Observations

Typically nucleophiles can react with fluoro-olefins[9-25] to produce a carbanion intermediate which subsequently acquires a proton (nucleophilic addition) or eliminates a halide ion either from the carbon atom which was originally attacked by the nucleophile (vinylic substitution) or from another carbon atom bonded to the carbanionic centre (allylic substitution). Further reactions can occur to produce polysubstitution derivatives. Normally no one pathway is followed to the exclusion of others, as illustrated by the reactions of perfluorocyclohexene[17,21], which undergoes both allylic and vinylic substitution to produce mono and disubstituted products. Where the nucleophile bears an active hydrogen atom dehydro-fluorination follows allylic substitution. Other polyfluorinated cyclic olefins react similarly[14,16,18,20,22].

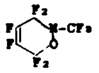
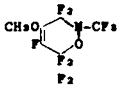
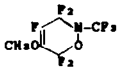
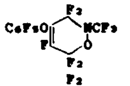
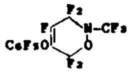
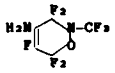
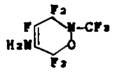
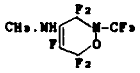
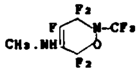
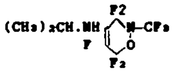
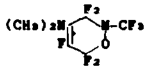
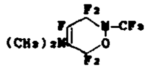
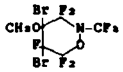
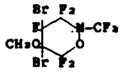
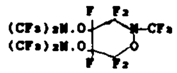


Relatively few studies have been undertaken on the reaction of tertiary amines with fluorinated cyclic olefins: betaines of type (3) resulted from reaction between tertiary amines and perfluorocyclobutene with subsequent hydrolysis[25,26].



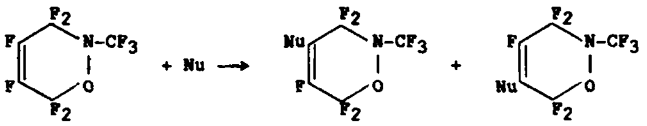
(3)

Reaction of oxazine (1) with a variety of oxygen and nitrogen nucleophiles (see Table on next page) gave in each case a mixture of the 4- and 5- substituted perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine) (4) and (5) respectively, with the latter isomer in preponderance. No allylic substitution products (6), or polysubstitution products, 3.

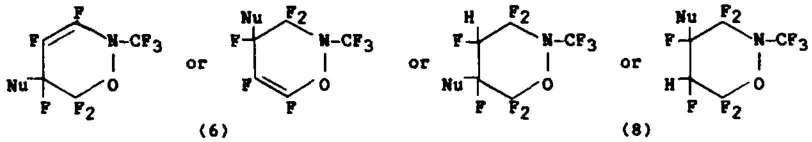
OXAZINE	TEMP (°C)	YIELD (%)	BP (°C/mm Hg)	n_D	I.r. C=C str (μ)	^{19}F nmr Chem.Shift of vinylic fluorine atoms (ppm to high field of T.F.A.)	ELEMENTAL ANALYSIS					
							REQUIRE			FOUND		
							C	H	N	C	H	N
	20	86	52/760	1.2920	5.67	80.1 82.1	-	-	-	-	-	-
 	60	15 60	113/761	1.3210	5.80	90.9 93.1	26.4	1.1	5.1	26.1	1.4	4.9
 	160	23 47	189/752	1.3776	5.75	70.9 (lost under aromatic fluorine peaks)	29.1	-	3.4	29.1	-	3.4
 	-78	15 59	31/1	1.3469	5.75	93.3 97.0	23.3	0.8	10.9	23.6	1.1	10.0
 	-78	18 55	50/1	1.3624	5.79	100.0 102.2	26.3	1.5	10.3	26.0	1.6	10.1
 	-78	19 57	56/1	1.3786	5.80	97.2 99.1	32.0	2.7	9.3	33.2*	3.0*	10.2
 	-78	1 72	49/1	1.3718	5.91	88.1 92.9	29.1	2.1	9.8	29.7	2.4	9.7
 	60/uv	20 80	184/762	1.4054	-		16.6	0.7	3.2	16.9	0.8	2.9
	20	98	155/761	1.2995	-	-	18.1	F 66.8	6.8	18.0	F 67.1	6.8

* Average of five experiments

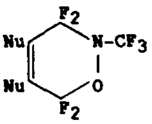
(e.g. 7) were observed. From studies with methoxide ions there were some indications for the presence of small amounts of addition products (8 where Nu = MeO).



(1) (4) (5)



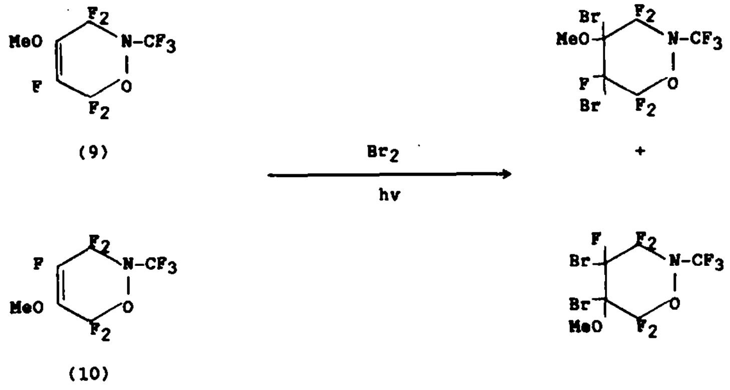
(6) (8)



(7)

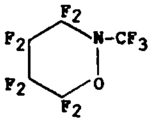
Furthermore, isomerisation could not be induced by treatment of either the parent oxazine (1) or the methoxy derivatives (4 and 5 where Nu = MeO) with fluoride ions. All this is at variance with nucleophilic reactions reported for other fluorinated cyclic olefins which, e.g. tend to react with alkoxides to yield vinyl and allyl ethers[17]. It is also noted that perfluorocyclohexene reacts rapidly with alkoxides at room temperature with the liberation of heat, whereas under analogous conditions oxazine (1) was recovered quantitatively: heating was required to effect reaction.

Although the 4- and 5- methoxy 3,3,4,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2$\underline{H}$-1, 2-oxazines could not be separated by g.l.c. they were identified by i.r. and n.m.r. spectroscopy, mass spectrometry and elemental analysis. The ratio of 4- and 5- vinyl substitution was ascertained from the relative peak intensities of the vinylic fluorine atoms in the F^{19} nmr spectrum. Furthermore, photochemical bromination of the mixture of 4- and 5-methoxy oxazines (9) and (10) yields a mixture of the corresponding bromine adducts which was characterised by ir and nmr spectroscopy, mass spectrometry and elemental analysis and which was resolved by g.l.c. into 2 peaks with intensity ratios of 1:4.

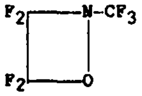


Our findings that oxazine (1) undergoes substitution with methoxide ions mainly at the 5-position conflict with those of Yakubovich et al[27]. These authors report the 4-methoxy oxazine (9) as the product from reaction of oxazine (1) with potassium methoxide and they do not mention the 5-isomer (10). When we repeated their experiment the 4- and 5-methoxy derivatives were again obtained in 1:4 ratio.

The inertness of the $-\overset{\overset{CF_3}{|}}{N}-O-$ group in the ring towards attack by methoxide ions was illustrated by the quantitative recovery of perfluoro (tetrahydro-2-methyl-2*H*-1,2-oxazine) (11) and perfluoro-(2-methyl-1,2-oxazetidine) (12) when these compounds were treated with methoxide ions under forcing conditions.

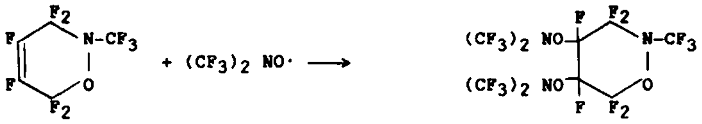


(11)



(12)

The stability of the ring structure towards UV radiation and free-radicals was confirmed by photolysis and by reaction with bis(trifluoromethyl)nitroxide. Hence, UV irradiation of oxazine (1) in a sealed tube for 100 hrs resulted in a 96% recovery. Also oxazine (1) and bis(trifluoromethyl)nitroxide in a 1:2 molar ratio reacted to yield 4,5-di(*N*,*N*-bistri-fluoromethylnitroxy)-3,3,4,5,6,6-hexafluoro-2-trifluoromethyl-tetrahydro-2*H*-1,2-oxazine(13) in 98% yield with no evidence of attack on the $.N(CF_3).O.$ part of the molecule.



(13)

Oxazine (1) produced only the 4- and 5- amino derivatives (plus a small amount of intractable oil) on reaction with ammonia, primary or secondary aliphatic amines. No reaction occurred between oxazine (1) and pentafluoroaniline, or its sodium salt. Similarly, (1) was inert to aniline at 40°, and under forcing conditions it produced an intractable black tar. Oxazine (1) remained unchanged when kept with trimethylamine at 20° for 18 hr.

On the basis of our findings, the oxazine (1) does not appear to behave as a typical cyclic fluoro-olefin in its reactions with nucleophiles.

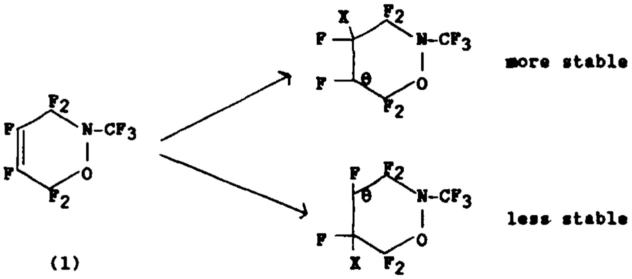
Thus:

1) More forcing conditions are required to effect reactions between alkoxides and (1) than with perfluorocyclohexene.

2) No polysubstitution products are formed.

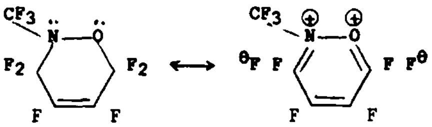
3) No double-bond rearrangement occurs, nor could it be induced in the parent oxazine or the methoxy derivatives. We note, however, that this may simply reflect a greater thermodynamic stability of the 4,5 unsaturated oxazine structure as compared with the 3,4 and 5,6 isomers which correspond to enamine and enol ether structures respectively.

4) Since the oxygen atom is rather more electronegative than the N-CF_3 moiety, the oxazine (1) would be expected to give predominantly 4-substituted products, derived from the more stable carbanion, rather than predominantly 5-substitution as observed:



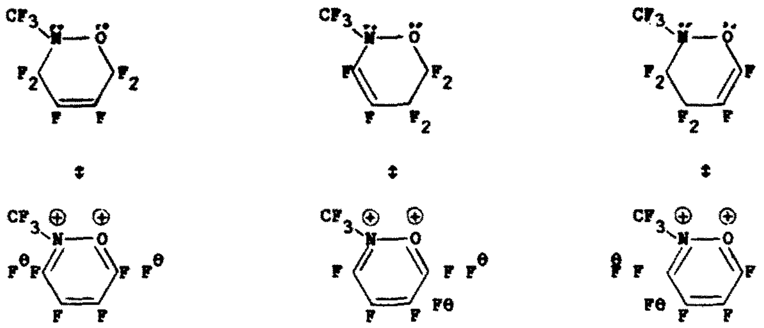
Mechanistic Interpretation

The relative stability of (1) towards certain nucleophiles seems, from inspection of Dreiding models, unlikely to be due to steric hinderance of the double bond by the CF_3 group. However, it may be explained in terms of negative hyperconjugation[7,8] involving the lone pairs on the nitrogen and oxygen atoms and the fluorine atoms in the 3- and 6-positions. This hyperconjugation gives a degree of aromatic character to the oxazine ring system, thus:



The two fluorine atoms in the 3 position can only participate equally in hyperconjugation with the nitrogen lone pair when the ring is planar. Thus, in the more likely half-chair conformation, the quasi-axial fluorine atom in the 3 position is better able than its quasi-equatorial partner to participate in hyperconjugation because its σ* (C-F) is more nearly coplanar with the nitrogen lone pair orbital (cf the well known anomeric effect[8,28-31]). However, the quasi-equatorial fluorine atom in the 3 position is not excluded entirely from involvement in hyperconjugation since its σ* (C-F) orbital is not orthogonal to the nitrogen lone pair orbital. An analogous argument applies to hyperconjugation involving the oxygen atom lone pairs and the fluorine atoms in the 6 position.

The double bond isomers of the oxazine could also have partial aromatic character due to negative hyperconjugation, but the degree of stabilisation will be less because of the greater proximity of like charges:



Thus, negative hyperconjugation can explain why (1) cannot be isomerised or converted to allylic substitution products. Partial aromaticity would also explain the apparent stability of (1) towards photolysis and its greater thermal stability compared with that of the saturated counterpart (11),[1,32].

The shift in the C-N and C-O stretches in the i.r. spectrum to lower wavelengths for (1) compared with those for (11) is also consistent with some aromatic character associated with (1):

I.R. Stretching Frequencies (wavelengths) for C-N and C-O bonds

Compound / Bond	1	11
C-N	10.29	10.31
C-O	9.20	9.47

Nucleophilic substitution at vinylic carbon is generally accepted to involve attack of the π^* orbital by the nucleophile with formation of a carbanionic centre. Rotation about the originally double-bond with inversion at the carbanionic centre allows the leaving group and the carbanion lone pair to become anti-periplanar and the leaving group can then be eliminated[4]. This general mechanism covers a spectrum of pathways ranging from stepwise (involving long-lived carbanions) to concerted (where the carbanionic centre never develops a full negative charge and π bonding between the originally olefinic carbon atoms is never completely lost[5]).

In the case of perfluorocyclohexene, interaction between the nucleophile and the π^* orbital can lead initially to a carbanion whose lone pair is axial and anti-periplanar to both the nucleophile and the originally allylic fluorine atom which is vicinal to it. Thus, allylic substitution can arise with minimum conformational change. For vinylic substitution, inversion at the carbanion is required causing the ring to flip to its alternative, chair conformation (which is favoured since most nucleophiles are larger than fluorine) from which either vinylic or allylic fluorine atoms can be expelled. Hence the observed vinylic and allylic substitution reactions of perfluorcyclohexene can be rationalised.

In the case of reactions with oxazine (1) however, there are 3 important differences:

1. The allylic fluorine atoms in oxazine (1), compared with their counterparts in perfluorocyclohexene, possess a greater partial negative character as a result of hyperconjugation with the nitrogen and oxygen lone pairs. Nucleophilic attack on (1) is therefore somewhat hindered because of electrostatic repulsion between the nucleophile and the allylic fluorine atoms. Since nitrogen is a better lone pair donor than is oxygen such repulsions would be stronger from the fluorines in the 2- rather than 6-position. Thus oxazine (1) is less reactive than perfluorocyclohexene towards nuclophiles. Reaction at the 4-position is disfavoured more than reaction at the 5-position.

2. The LUMO associated with the axial originally allylic fluorine is the anti-bonding combination of σ^* (C-F) and the oxygen or nitrogen lone pair orbital, and is therefore of higher energy than σ^* (C-F). As a consequence, interaction of the originally allylic C-F LUMO with the carbanionic lone pair orbital is less favoured in the case of oxazine (1) than in the case of perfluorocyclohexene with the oxazine-derived carbanions being less able to be stabilised by hyperconjugation, and less able to expel an originally allylic fluorine atom.

3. Formation of the carbanion involves a loss of aromaticity in the case of oxazine (1).

These effects all tend to make oxazine 1 less reactive than perfluorocyclohexene towards nucleophiles and effects 2 and 3 make it less likely to react via a fully developed carbanion. Effect 1. above favours 5-substitution whereas effect 2. favours 4-substitution. Our observations that 5-substitution predominates suggests effect 1. outweighs effect 2. This seems most plausible for a concerted reaction pathway in which the carbanionic centre does not develop a full negative charge thereby minimising loss of aromaticity in the transition state.

Finally, we note that a simple S_N2 mechanism in which the nucleophile HOMO interacts with σ^* (vinylic C-F) in a front-side fashion cannot be ruled out. Front-side bonding interaction between a nucleophile HOMO and σ^* (C-leaving group) orbital will be maximised when the σ^* orbital is lowered in energy and when the carbon atom is the major contributor to σ^* (C-leaving group). Because of the high electronegativity of fluorine, both of these criteria apply in the case of fluoro-olefins. Thus, if simple S_N2 vinylic substitution occurs at all it should be found in fluoro-olefins, particularly where, as with oxazine (1), there are factors disfavouring the pathways involving attack on the π^* orbital.

EXPERIMENTAL

Preparation of Perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine)

A mixture of hexafluorobutadiene (6.97g, 43.0 mmoles) and trifluoronitrosomethane (4.65g, 47.0 mmoles) was sealed in 250ml Pyrex reaction tube and kept at 20° for 16 hr, after which time the blue colour had almost completely vanished. The volatile produts were vented to the system and fractionated to give the following fractions:

1) -196° trap: Unreacted trifluoronitrosomethane (0.455g, 4.61 mmoles; 9% recovery).

2) -78° trap: A colourless liquid (9.50g, 36.4 mmoles; 86% yield based on C_4F_6 consumed) shown by molecular weight, and ir spectroscopy to be perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) (Found: M, 260, Calc. for C_5F_9NO : M 261), bp 51°/759 mm (lit[2], bp 52.4°/760 mm).

In the reaction tube there remained a colourless, involatile copolymer (1.60g, 14%).

Reactions of perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine)

A. With Caesium Fluoride

Perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) was heated with caesium fluoride in an attempt to cause isomerisation.

i) At 100°

Caesium fluoride (ca 1g) was heated, in vacuo, at 200° (oil bath) in a 250ml Pyrex reaction tube for 6 hr to remove moisture. Perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) (1.0g, 3.80 mmoles) was condensed into the tube at -196°; the tube was then sealed and heated at 100° for 16 hr. The volatiles were vented to the system and fractionated by trap-to-trap condensation, in vacuo, to give:

1) -78° trap: A fraction (1.0g, 3.80 mmoles; 100% recovery) shown by ir and nmr spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine).

ii) At 100° in Sulpholane

In another experiment caesium fluoride (ca 1g) was dried as described above and sulpholane (5ml) then added (in a dry-box under a blanket of nitrogen), and, after degassing, perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) (1.0g, 3.80 mmoles) condensed in at -196°. The tube was heated at 100° for 16 hr and the volatiles then vented to the system and fractionated, to give:

1) -78° trap: A fraction (0.99g, 3.79 mmoles; 99% recovery) shown by ir and nmr spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2H- 1,2-oxazine).

iii) At 200°

Similarly, when perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) (0.99g, 3.79 mmoles) and dry caesium fluoride were heated together in a sealed tube, in vacuo, at 200° for 20 hr, the volatile matter (0.99g, 3.79 mmoles; 100% recovery) was shown by ir and nmr spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine).

B. With Sodium Methoxide

i) At 20°

Sodium (0.15g, 7mg. atoms) was allowed to react with excess dry methanol (1.84g, 57.5 mmoles) in a 10ml, 2-necked flask fitted with a condenser (with drying tube) and dropping funnel containing perfluoro-(3,6-dihydro-2- methyl-2H-1,2-oxazine) (1.44g, 5.50 mmoles). The oxazine was added dropwise to the stirred sodium methoxide solution over a period of 15 min at 20° and the solution stirred for a further hour. The contents of the flask were poured into water (10ml) and the bottom layer was separated and dried ($MgSO_4$), to give a colourless liquid (1.41g, 5.40 mmoles; 98% recovery) shown by glc, molecular weight and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine).

ii) At 60° in a Closed System

Sodium (0.15g, 7mg atoms) was allowed to react with an excess of dry methanol (1.60g, 50.0 mmoles) in a 50ml Pyrex reaction tube. After the tube and contents had been degassed, perfluoro-(3,6-dihydro-2-methyl-2H-1,2- oxazine) (1.44g, 5.50 mmoles) was condensed in at -196°. The tube was then heated at 60°, with agitation (polymerisation tank) for 12 hr; the yellow liquid product was poured into water (10ml), and the bottom layer was separated and dried ($MgSO_4$), to yield a colourless liquid (1.30g) which was separated by preparative glc (4m dinonyl phthalate at 100°) into three fractions:

Fraction 1: This was unchanged oxazine (trace).

Fraction 2: A high boiling liquid (83%) identified as an isomeric mixture of 5-methoxy-3,3,4,6,6-pentafluoro-(2-trifluoromethyl-3,6- dihydro-2*H*-1,2- oxazine) (80%) and 4-methoxy-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2*H*-1,2-oxazine) (20%) (1.13g, 4.14 mmoles; 75%) (Found: C, 26.1; H,1.4; N, 4.9%; *M*, 270. $C_6H_3F_8NO_2$ requires C, 26.4; H, 1.1; N, 5.1%; *M*, 273), b.p. 113°/761mm (Siwoloboff), n_D^{20} 1.321. The presence of the two isomers was indicated by several features in the nmr spectrum, the most striking being the presence of *two* vinylic fluorine atoms (approx in the ratio 4:1) with chemical shifts at 89 and 91 ppm to high field of trifluoroacetic acid. The ir spectrum showed absorption bands at 3.26, 3.23, 3.35 (w, C-H str), 5.80 (vs, C=C str), 6.84 (s, C-H def), 7.40-8.69 (vs, C-F str), 9.30 (s, N-O str), and 10.53μ (s, C-N str). The mass spectrum showed a parent peak at *m/e* 273 (67% rel abund) and a fragmentation pattern consistent with the structure. The presence of C=C unsaturation was also shown by reaction of the mixture with bromine.

Fraction 3: An unidentified compound (16%) having a similar ir spectrum to that of the above ethers but containing no unsaturation, possibly an isomeric mixture of the saturated ethers (VII).

iii) *At 60° in an Open System*

In view of the difference between the authors' results and the other publication describing the reaction of sodium methoxide with perfluoro-(3,6- dihydro-2-methyl -2*H*-1,2-oxazine) to yield 4-methoxy-3,3,5, 6,6-pentafluoro-2-trifluoromethyl -3,6-dihydro-2*H*-1,2-oxazine in 78% yield, the authors repeated the Russian experiment, as described below.

Perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine) (2.00g, 7.60 mmoles) was added dropwise over a period of 30 min to a well-stirred mixture of KOH pellets (0.80g, 14.3 mmoles) and dry methanol (10ml) contained in a 25ml, 2-necked round-bottom flask fitted with a reflux condenser and dropping funnel (the flask becoming slightly warm). When the addition was complete, the flask was heated to 50° for 3 hr. The product was cooled, treated with water (15ml), and the lower layer separated, washed with water (2 x 5ml), dried ($MgSO_4$) and distilled to give a colourless liquid (1.80g); this was shown by glc analyses (4m dinonyl phthalate at 100°) to consist of two fractions, *viz*:

Fraction 1: A high boiling liquid shown by nmr to consist of both the 4- and 5-methoxy-oxazines (0.80g, 2.90 mmoles; 74%) with the latter predominating.

Fraction 2: A high boiling liquid (0.16g, 9%) with an ir spectrum identical to that of unidentified compound obtained in (ii).

C) *With Ammonia*

i) *At 20°*

The oxazine (1.50g, 5.24 mmoles), ammonia (0.27g, 15.7 mmoles) and dry ether (10ml) were condensed, *in vacuo*, into a 250ml Pyrex reaction tube at -196°. The tube was allowed to warm to 20° and held at this temperature for 15 hr and the volatiles fractionated by trap-to-trap condensation, to give:

1) *-196° trap*: A fraction (0.06g, 3.71 mmoles; 23% recovery) shown by ir spectroscopy to be ammonia.

2) *-78° trap*: A fraction shown by glc analysis (2m dinonyl phthalate at 20°) and ir spectroscopy to be ether contaminated with traces of perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

3) *-23° trap*: A colourless, unstable liquid identified as an isomeric mixture of 4-amino-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2*H*- 1,2-oxazine (20%) and 5-amino-3,3,4,6,6-pentafluoro-2-trifluoromethyl-3,6- dihydro-2*H*-1,2-oxazine (80%) (0.61g, 2.36 mmoles; 41%) (Found: C, 23.6; H, 1.1; N, 10.7%; M, 258. $C_5H_2F_8N_2O$ requires C, 23.3; H, 0.8; N, 10.9%; *M*, 258), bp 33°/1mm, n_D^{20} 1.3469. Identification was affected by ^1H and ^{19}F nmr spectroscopy and by the molecular fragmentation pattern of its mass spectrum . The ir spectrum of the mixture showed absorption bands at 2.85, 2.92 (m, N-H str), 5.75 (s, C=C str), 6.17 (m, N-H def), 7.09-9.01 (s, C-F str), 9.35 (m, N-O str), 10.64 (m, C-N str), and 13.93μ (s, CF_3 def).

In the tube there remained a brown oil (*ca* 0.4g) which was not examined.

ii) *At -78°*

In a similar experiment, the oxazine (2.00g, 7.62 mmoles), ammonia (0.30g, 17.7 mmoles) and ether (10ml) were stored, *in vacuo*, in a 250ml Pyrex tube at -78° for 1 week followed by 5 hr at room temperature. The volatiles were then vented to the system and fractionated to give:

1) *-196° trap*: A fraction (0.02g, 1.00 mmoles; 6% recovery) shown by molecular-weight and ir spectroscopy to be ammonia.

2) *-78° trap*: A fraction (*ca* 10ml) shown by glc analysis (2m dinonyl phthalate at 20°) to be ether contaminated with a trace of oxazine.

3) *-23° trap*: A fraction (0.73g, 2.83 mmoles; 74%) identified as an isomeric mixture of the 4- and 5-amino substituted oxazines.

In the reaction tube there remained an unidentified brown tar (*ca* 0.1g).

D) *With Isopropylamine*

i) *At 20°*

The oxazine (1.12g, 4.29 mmoles), isopropylamine (0.76g, 13.0 mmoles), and ether (10ml) were sealed, *in vacuo*, in a 250ml Pyrex tube at -196°. The tube was allowed to warm to 20° and left 1hr after which time the contents were poured into water (10ml) to remove the amine hydrofluoride produced and the ether layer separated, washed with water(2 x 5ml), dried ($MgSO_4$) and the ether then removed at the pump to leave a yellow oil which when distilled gave a colourless distillate and a brown oily tar. The colourless liquid was identified as an isomeric mixture of 4-isopropylamino-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2H1,2-oxazine (25%) and 5-isopropylamino-3,3,4,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2H1,2- oxazine (75%) (0.43g, 1.42 mmoles; 33%) (Found: C,33.0, 33.9, 33.4, 32.7, 33.0; H, 2.7, 3.2, 2.9, 2.9, 3.4; N, 9.3, 8.2, 9.5, 14.8, 9.2%. $C_8H_8F_8N_2O$ requires C, 32.0; H, 2.7; N, 9.3%), bp 56°/1mm, n_D^{20} 1.3786. Although the compound decomposed rapidly at room temperature and an analytically pure sample could not be isolated by standard techniques (prep glc, *etc*), the structure of the compound was deduced with certainty from spectroscopic data. Thus the ir spectrum showed adsorption bands at 2.91 (s, N-H str), 3.35, 3.40, 3.47 (m, C-H str), 5.80 (s, C=C str), 6.60 (s, N-H def), 6.60, 6.85 (s, C-H def), 7.18-9.05 (s, C-F str), 9.35 (s, N-O str), 10.28 (s, C-N str), and 13.89μ (s, CF_3 def). The ^1H and ^{19}F nmr spectra were consistent with the proposed structures and again indicated that the two isomers were present. The molecular fragmentation pattern of its mass spectrum was also consistent with the proposed structure with a parent peak at *m/e* 300 (1.00% rel abund) ($C_8H_8F_8N_2O$ requires *m*, 300).

ii) *At -78°*

The oxazine (2.23g, 8.60 mmoles), isopropylamine (1.62g, 27.5 mmoles), and ether (15ml) were sealed, *in vacuo*, in a 250ml Pyrex reaction tube at -196°. The tube was then stored at -78° (cardice/meths bath) for 1 week, and the reaction worked up as before to give the isomeric mixture of 4- and 5-iso-propylamino-oxazines (1.95g, 6.54 mmoles; 76%) and a yellow oil (*ca* 0.1g).

E) *With Methylamine at -78°*

To confirm the structure of the secondary amine produced in the reaction between perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) and isopropylamine, the reaction was repeated using methylamine as the primary amine with the hope of isolating an analytically pure product.

The oxazine (1.94g, 7.41 mmoles), methylamine (3.41g, 0.11 moles) and ether (5ml) were sealed, *in vacuo*, in a 250ml Pyrex tube at -196°. The tube was stored at -78° for 16hr and the volatile vented to the system and fractionated to give:

1) *-196° trap*: A fraction shown by molecular weight and ir to be unchanged methylamine (2.79g, 0.09 mmoles; 81% recovery).

2) *-78° trap*: Ether (5ml) shown by glc and ir to be contaminated with a trace of unchanged oxazine.

3) -23° trap: An unstable, colourless liquid identified as an isomeric mixture of 4-methylamino-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6- dihydro-2H-1, 2-oxazine (25%) and 5-methylamino-3,3,4,6,6-pentafluoro-2- trifluoromethyl-3,6-dihydro-2H-1,2-oxazine (75%) (1.46g, 5.41 mmoles; 73%) (Found: C, 26.0; H, 1.6; N, 10.1%; M, 272. $C_6H_4F_8N_2O$ requires C, 26.3; H, 1.5; N, 10.3%; M, 272), bp 50°/1mm, n_D^{21} 1.3624. Again the liquid decomposed rapidly at room temperature to give a brown oil and no attempt was made to separate the isomers by glc. The structure of the products was also deduced from spectroscopic data. The ir spectrum showed absorption bands at 2.89, 2.98 (m, N-H str), 3.27, 3.35, 3.38, 3.42, 3.51 (w, C-H str), 5.79 (s, C=C str), 6.56 (m, N-H def), 7.32-8.85 (s, C-F str), 9.01 (s, N-O str), 10.42 (s, C-N str), 13.88µ (s, CF_3 def). The ^1H and ^{19}F nmr were con- sistent with the suggested structure and clearly showed the presence of two isomers, and the molecular fragmentation pattern of its mass spectrum was in accord with the proposed structure giving a molecular weight of 272.

In the tube there remained a yellow oil which besides giving a poor ir was not further investigated.

F) With Dimethylamine at -78°

A mixture of oxazine (2.96g, 11.2 mmoles), excess dimethylamine (4.50g, 100 mmoles) and ether (10ml) were stored, *in vacuo*, in a 250ml Pyrex tube at -78° for 3hr. The tube was then allowed to warm to room temperature and left for 30 min after which time the volatiles were vented to the system and fractionated to give:

1) -196° trap: A fraction (3.19g, 71.1 mmoles; 71% recovery) shown by molecular weight and ir spectroscopy to be dimethylamine.

2) -78° trap: A fraction shown by ir spectroscopy to be a mixture of ether contaminated with traces of oxazine and dimethylamine.

In the tube there remained a yellow oil which when distilled gave a colourless liquid identified as 5-dimethylamino-3,3,4,6,6-pentafluoro-2- tri-fluoromethyl-3,6 -dihydro-2H-1,2-oxazine (99%) plus a trace of 4-dimethyl-amino-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2H-1,2-oxazine (ca 1%) (2.35g, 8.21 mmoles; 73% yield) (Found: C, 29.7; H, 2.4; N, 9.7%; M, 286. $C_7H_6F_8N_2O$ requires C, 29.4; H, 2.1; N, 9.8%; M, 286), bp 49°/1mm, n_D^{20} 1.3718. The ^{19}F nmr spectrum indicated that the product was mainly the 5-dimethylamino-oxazine with only a trace of the 4-dimethylamino isomer. The ir spectrum was consistent with the proposed structure showing absorption bands at 3.38, 3.40, 3.47 (m, C-H str), 5.91 (s, C=C str), 6.69, 6.85 (m, C-H def), 7.41-8.97 (s, C-F str), 9.43 (s, N-O str), 10.36 (s, C-N str), 13.88µ (s, CF_3 def). A significant feature of the molecular fragmentation pattern of the mass spectrum was the parent peak at m/e 286 corresponding to the molecular $C_7H_6F_8N_2O$.

G) Attempted Reaction with Pentafluoroaniline

A mixture of oxazine (1.10g, 4.24 mmoles) and pentafluoroaniline (2.00g, 10.9 mmoles) in dimethylformamide (10ml) was refluxed for 5hr in 50ml round-bottom flask fitted with a condenser. The volatile material was transferred to the system and fractionated to give:

1) -78° trap: A fraction (1.08g, 4.19 mmoles; 98% recovery) shown by molecular weight and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine).

2) -23° trap: A fraction shown by ir spectroscopy to be dimethylformamide.

H) Attempted Reaction with Aniline

i) At 40°

Freshly distilled aniline (1.53g, 16.4 mmoles), oxazine (1.156g, 4.42 mmoles), and ether (5ml) were heated at 40° in a 50ml Pyrex reaction tube for 70hr (polymerisation tank) and the volatiles fractionated by trap-to- trap condensation to give:

1) -78° trap: A fraction shown by glc analysis (2m dinonyl phthalate at 20°) to be a mixture of ether and unchanged perfluoro-(3,6-dihydro-2-methyl-2H-1,2-oxazine) (1.11g, 4.22 mmoles; 96% recovery).

2) -23° trap: A fraction (1.50g, 16.1 mmoles; 98% recovery) shown by glc analysis and ir spectroscopy to be unchanged aniline.

ii) At 70°

In a similar experiment, aniline (1.50g, 16.1 mmoles), oxazine (1.15g, 4.41 mmoles), and ether (5ml) were sealed, *in vacuo*, in a 50ml Pyrex tube and heated at 70° with agitation for 24hr during which time the contents of the tube became dark coloured. The contents of the tube were distilled and under reduced pressure to give aniline (0.84g, 9.00 mmoles; 56% recovery) and leaving behind in the flask a black tar (*ca* 1.5g) from which nothing could be isolated by sublimation, *in vacuo*, solvent extraction, or column chromatography. The ir spectrum of the tar itself proved to be featureless.

I) With the Sodium Salt of Pentafluoroaniline

The sodium salt of pentafluoroaniline was prepared by the method described by Brooke and Rutherford in a recent publication[33]. Thus, a solution of pentafluoroaniline (0.67g, 3.80 mmoles) in dry tetrahydrofuran (5ml) was added to a cold (-20°) solution of sodium hydride (0.09g, 3.83 mmoles) in dry tetrahydrofuran (5ml) contained in a 25ml 2-necked, round-bottomed flask. The white suspension so produced was stirred for 4hr at -20° and eventually darkened somewhat.

The oxazine (0.92g, 3.52 mmoles) was added to the white suspension and the mixture was refluxed for 5hr. The volatiles were transferred to the system and fractionated, to give:

1) -78° trap: A fraction (0.92g, 3.51 mmoles; 99% recovery) shown by molecular weight and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

2) -64° trap: A fraction (*ca* 4g) shown by ir spectroscopy glc analysis (2m silicone oil at 20°) to be tetrahydrofuran.

J) With Sodium Pentafluorophenate

i) In Tetrahydrofuran (THF) at 80°

Sodium (0.15g, 6.52mg atoms) was added in small pieces to a solution of pentafluorophenol (1.37g, 7.44 mmoles) in ether (10ml). On completion of the reaction the contents were transferred to a 50ml reaction tube and the ether removed at the pump. Dry THF (10ml) was condensed into the tube, followed by oxazine (1.65g, 6.34 mmoles). The tube was heated at 80° for 16hr and the volatiles transferred to the vacuum system and fractionated, to give:

1) -78° trap: A liquid shown by ir spectroscopy and glc analysis (2m dinonyl phthalate at 20°) to be tetrahydrofuran and unchanged oxazine (1.62g, 6.21 mmoles; 98% recovery).

ii) In Sulpholane at 160°

In view of the inertness of the oxazine towards sodium pentafluorophenate in THF it was decided to use a dipolar aprotic solvent (Sulpholane) which solvates the nucleophile to a much less degree.

Thus, an ethereal suspension of sodium pentafluorophenate (1.36g, 7.40 mmoles), prepared as described above, was transferred to a 50ml Pyrex tube and the ether removed at the pump at 80°. Dry sulpholane (10ml) was introduced (in a dry-box) and, after the system had been degassed, the oxazine (2.59g, 9.92 mmoles) was added. The tube was heated at 160° in a rocking furnace for 40hr and the condensable material fractionated by trap-to-trap condensation to give:

1) -78° trap: A fraction (1.89g, 7.24 mmoles; 73% recovery) shown by molecular weight, glc analysis (2m dinonyl phthalate at 20°) to be unchanged perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

2) -23° trap: A colourless liquid (0.80g, 1.89 mmoles, 70% recovery) identified as an isomeric mixture of 4-pentafluoro-phenoxy-3,3,5,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2*H*-1,2-oxazine (33%) and 5-pentafluoro-phenoxy-3,3,4,6,6-pentafluoro-2-trifluoromethyl-3,6-dihydro-2*H*-1,2-oxazine (67%) (Found: C, 29.1; N, 3.4%; *M*, 425. $C_{11}F_{13}NO_2$ requires C, 29.1; N, 3.4%; *M*, 425), bp 189°/752mm, (Siwoloboff), n_D^{21} 1.3776. The ir spectrum showed absorption bands at 5.75 (s, C=C str), 6.56 (s, $C-C_{arom}$ str), 7.28-8.85 (s, C-F str), 9.28 (s, N-O str), 10.26 (s, C-N str), and 13.79μ (s, CF_3 def). The ^{19}F nmr of the mixture and the fragmentation pattern of its mass spectrum were also consistent with the proposed structure.

K) *With Bistrifluoromethylnitroxide*

Perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine) (0.81g, 3.18 mmoles) and bistrifluoromethylnitroxide (1.07g, 6.36 mmoles) were sealed in a 50ml Pyrex tube and left at room temperature for 3 months; the purple colour of the nitroxide radical faded considerably during this period. The volatiles were fractionated by trap-to-trap condensation to give:

1) *-196° trap*: A fraction (0.26g, 1.54 mmoles; 24% recovery) shown by molecular weight and ir spectroscopy to be bistrifluoromethylnitroxide.

2) *-78° trap*: A fraction (0.20g, 0.76 mmoles, 24% recovery) shown by molecular weight, glc analysis (2m dinonyl phthalate at 20°) and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

In the tube there remained a colourless oil (1.40g, 2.35 mmoles; 98% recovery) identified as 4,5-di(*N*,*N*-bistrifluoromethylnitroxy)-3,3,4,6,6-hexafluoro -2-trifluoromethyl-3,6-tetrahydro-2*H*-1,2-oxazine) (Found: C, 18.0; N, 6.8; F, 67.1%, *M*, 597. $C_9F_{21}N_3O_3$ requires C, 18.1; N, 7.0; F; 66.8%; *M*, 597), bp 155°/761mm (Siwoloboff), n_D^{21} 1.2995. The ^{19}F nmr spectrum of this product and the fragmentation pattern of its mass spectrum were consistent with the proposed structure. The ir spectrum showed absorption bands at 7.57-8.85 (s, C-F str), 9.39 (s, N-O str), 10.31 (s, C-N str), 13.99μ (s, CF_3 def).

L) *Photolysis*

The oxazine (1.00g, 3.80 mmoles) was sealed, *in vacuo*, in a 300ml silica glass tube with the bottom third blackened to prevent further photolysis of products, and irradiated with ultraviolet light (500 W Hanovia lamp) at a distance of 18" for 100 hr. The volatiles were fractionated by trap-to-trap condensation to give:

1) *-196° trap*: A trace fraction shown by ir spectroscopy to be silicon tetrafluoride.

2) *-78° trap*: A fraction (0.96g, 3.68 mmoles; 96% recovery, shown by molecular weight, glc analysis (2m dinonyl phthalate at 20°) and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

In a similar experiment the oxazine (100g, 3.80 mmoles) was irradiated for 1 month and the volatile matter fractionated in the system to give:

1) *-196° trap*: A trace fraction identified by ir spectroscopy as silicon tetrafluoride.

2) *-78° trap*: A fraction (0.89g, 3.40 mmoles; 89% recovery) shown by molecular weight, glc analysis (2m dinonyl phthalate at 60°) and ir spectroscopy to be unchanged perfluoro-(3,6-dihydro-2-methyl-2*H*-1,2-oxazine).

In the reaction tube there remained a high-boiling yellow liquid, (0.2g) shown by ir spectroscopy to contain the group $C\equiv N$ (4.45μ, C=O (5.41μ), C=C (5.71μ), and C-F (7.15-9.62μ). Glc analysis (3m silicone oil at 80°) showed the presence of at least eight components; decomposition of some of the compounds took place on the column and none were isolated or identified.

Reactions of the Isomeric Mixtures of 4- and 5-Methoxypentafluoro-2-trifluoromethyl-3,6-dihydro-2H-1,2-oxazines

A) *With Bromine*

A mixture of the ethers (0.30g, 1.09 mmoles) and excess bromine (1.60g, 10 mmoles) sealed, *in vacuo*, in a 10ml Pyrex tube was heated at 60° whilst being irradiated with soft ultraviolet light from a 300 W gas filled lamp for 6hr. The excess bromine (1.25g, 7.80 mmoles; 78% recovery) was vented to the system leaving behind in the tube a colourless oil (0.48g, 1.08 mmoles; 98% recovery) shown to be an isomeric mixtures of 4,5-dibromo-4- methoxy-3,3,5,6,6-pentafluoro-2-trifluoromethyl-tetrahydro-1,2-oxazine (20%) and 4,5-dibromo-5-methoxy-3,3,4,6,6-pentafluoro-2-trifluoromethyl -tetrahydro-1,2-oxazine (80%). (Found: C, 16.9; H, 0.8; N, 2.9%; *M*, 433.

$C_6H_3F_8Br_2NO_2$ requires C, 16.6, H, 0.7; N, 3.2%; *M*, 433), bp 184°/762mm, n_D^{22} 1.4054. Although the original unsaturated ethers could not be separated by glc the brominated ethers showed two peaks in the ratio 1:4 when subjected to glc analysis (2m dinonyl phthalate at 100°) but insufficient material was available for their separation by preparative glc. The ^1H and ^{19}F nmr spectra were complex but consistent with the proposed structures. Although a molecular ion was not obtained from the mass spectrum other features of the fragmentation pattern (such as P-79 and P-81) peaks supported the suggested structure. The ir spectrum showed absorption bands at 3.37 (m, C-H str), 6.82, 6.90 (m, C-H def), 7.66-8.89 (s, C-F str), 9.30 (s, N-O str), 10.37 (s, C-N str), 13.16μ (s, CF_3 def).

B) With Potassium Fluoride

A mixture of the ethers (0.50g, 1.15 mmoles), potassium fluoride (0.50g, 8.62 mmoles) and dimethylformamide (1ml) were shaken in a sealed tube at 60° for 5hr. After cooling, the tube was opened and the contents poured into excess water (10ml). The lower layer was separated, washed with water, dried ($MgSO_4$) and shown by glc analysis (2m dinonyl phthalate at 60°), ir and nmr spectroscopy to be an unchanged mixture of 4- and 5-methoxypentafluoro-2-trifluoromethyl-3,6-dihydro-2H-1,2-oxazine (0.45g, 1.04 mmoles; 90% recovery).

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