Fluorinated Aminooxazolines. Synthesis and Properties

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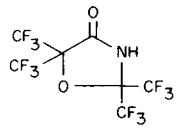
4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**3a**) was prepared from the reaction of sodium cyanide with hexafluoroacetone and hexafluoroacetone imine, and from the reaction of hexafluoroacetone cyanohydrin with the imine. Several other oxazolines were also prepared by related reactions of other fluoroketones and imines. The proton nmr spectrum of an ^{15}N-labeled sample of **3a** shows that it exists in solution primarily as the amino tautomer and not as the imino tautomer **3b**. Comparison of **3a** with the closely related, pharmacologically active 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**) has shown large differences in ΔH of complex formation and reactivity with electrophilic reagents.

In earlier studies aimed at the synthesis of heterocyclic compounds highly substituted with fluoroalkyl groups, it was found that the oxazolidinone **1** could be prepared by the reaction of sodium cyanide with two equivalents of hexafluoroacetone (1), and the aminoimidazoline **2** could be prepared from sodium cyanide and hexafluoroacetone imine (2).



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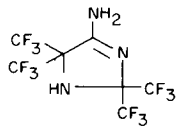

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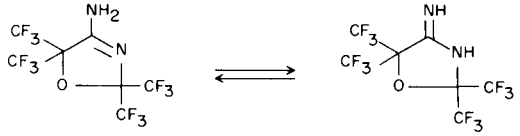


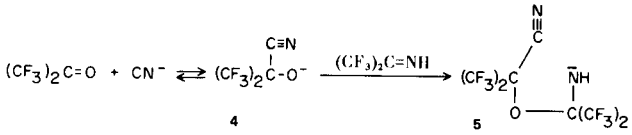
3a 3b

Since the aminoimidazoline **2** possesses pronounced physiological activity as a muscle relaxant (3), it was of interest to prepare the analogous aminooxazoline **3a**, which differs from **2** only in that the 1-NH is replaced with oxygen and which would be formally the adduct of one equivalent each of HCN, hexafluoroacetone and hexafluoroacetone imine.

Synthesis.

The oxazoline **3a** was prepared by the same general type of reaction used to prepare **1** and **2**. The sequential distillation of hexafluoroacetone and then hexafluoroacetone imine into a suspension of sodium cyanide in acetonitrile gave **3a** in 37% yield. This reaction was found to be general, and a number of new aminooxazolines were prepared utilizing four different fluoroketones, including hexafluoro-, pentafluoro-, tetrafluoro-, and chloropentafluoroacetone, and three fluorimines, including imines of hexafluoro-, pentafluoro-, and chloropentafluoroacetone (see Table I).

The preparation of aminooxazoline **3a** can be regarded as proceeding in at least two distinct steps. The first step is the addition of cyanide ion to hexafluoroacetone to form the salt of the cyanohydrin **4**. The second step involves the attack of the cyanohydrin anion on the fluorimine to give the intermediate anion **5** which cyclizes to anion **6**. This anion could then tautomerize to resonance-stabilized anion **7**, which upon acidification gives **3a**.



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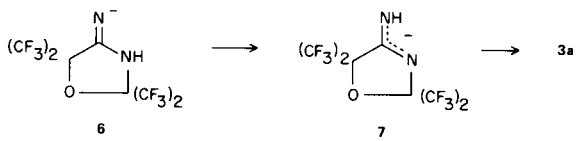

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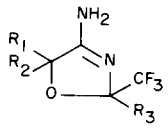
The yields of some of the aminooxazolines listed in Table I were lowered by formation of an oxazolidinone by-product from the reaction of two equivalents of ketone with cyanide ion. This by-product arises because the

TABLE I

4-Amino-3-oxazolines



Compound (a)						Yield		IR (KBr)
R_1	R_2	R_3	Ketone	Imine	Method	%	M.p. °C	μ
CF_3	CF_3	CF_3	$(CF_3)_2CO$	$(CF_3)_2C{=}NH$	A	37	136-138	5.89
					B	58		
CF_3	CF_2H	CF_3	$CF_3\overset{O}{\overset{\|}{C}}CF_2H$	$(CF_3)_2C{=}NH$	A	23	123-125	5.86
CF_2Cl	CF_2H	CF_3	$CF_2Cl\overset{O}{\overset{\|}{C}}CF_2H$	$(CF_3)_2C{=}NH$	A	29	101-103	5.91
$-CF_2CF_2CF_2-$		CF_3		$(CF_3)_2C{=}NH$	B	58	135-137	5.91
$-CF_2CF_2CF_2-$		CF_2H		$CF_3\overset{NH}{\overset{\|}{C}}CF_2H$	B	32	125-126	5.87
CF_2H	CF_2H	CF_2H	$CF_2H\overset{O}{\overset{\|}{C}}CF_2H$	$CF_3\overset{NH}{\overset{\|}{C}}CF_2H$	A	11	129-131	5.90
CF_2H	CF_3	CF_2H	$CF_3\overset{O}{\overset{\|}{C}}CF_2H$	$CF_3\overset{NH}{\overset{\|}{C}}CF_2H$	A	45 (b)	133-135	5.92
CF_3	CF_3	CF_2Cl	$(CF_3)_2CO$	$CF_3\overset{NH}{\overset{\|}{C}}CF_2Cl$	A	32	103-104	5.87

(a) Elemental analyses of these compounds checked with calculated values. (b) Mixture of *cis* and *trans* isomers.

formation of the cyanohydrin salt from sodium cyanide and the fluoroketone is a reversible reaction, and there is present at all times an equilibrium concentration of the ketone. Oxazolidinone formation was not noticed when hexafluoroacetone was used as the ketone, but was quite apparent when pentafluoroacetone and tetrafluoroacetone were used. The acidic oxazolidinones were easily removed from the aminooxazolines by extraction with aqueous 5% sodium hydroxide.

In order to minimize the difficulties involving sodium cyanide, an alternate method of synthesis was developed. The preformed cyanohydrin was treated with the fluorimine in the presence of an amine catalyst. This method avoided the extensive formation of oxazolidinones and resulted in higher yields of the aminooxazolines. Oxazoline **3a** was obtained in 58% yield, as contrasted with the 38% yield obtained by the sodium cyanide method. Aminooxazolines were also prepared from hexafluorocyclobutanone using this second procedure, even though the procedure using sodium cyanide was unsuccessful.

Structure Proof.

The skeletal structure of aminooxazoline **3a** was established by its hydrolysis to the known lactam **1** using the very vigorous conditions of 90% sulfuric acid at 200°. However, neither this hydrolysis nor the spectral data could be used to distinguish between the two possible tautomers (**3a** and **3b**). The ^1H nmr spectrum in acetone at 25° showed only a single broad band at 2.34 τ, which could be interpreted as being due to the amino hydrogens of **3a** or the rapidly exchanging hydrogens of **3b**. The ^{19}F nmr spectrum showed two septets (J = 5 Hz) at δ 73.7 and 78.4 ppm from fluorotrichloromethane, a spectrum which is very similar to that of the lactam **1** and the aminoimidazoline **2**.

This tautomer problem was solved by the same method used to establish the tautomeric identity of aminoimidazoline **2** (2). A sample of aminooxazoline **3a** containing a ^{15}N-labeled amino group was prepared from $NaC^{15}N$, hexafluoroacetone, and hexafluoroacetone imine. The ^1H nmr spectrum of this labeled sample in acetone showed

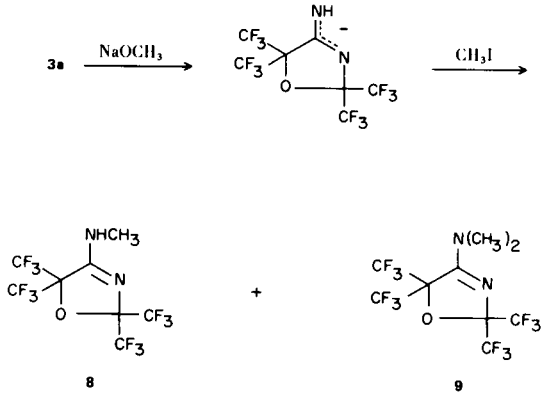
only a doublet with a spin-spin coupling constant of 93 Hz. A ^{15}N-^{1}H coupling of this magnitude is consistent with protons directly bound to ^{15}N (4) and therefore establishes the amino tautomer **3a** as the structure. The imino structure **3b** cannot be of major importance since the NH coupling would be expected to be a low value for the hydrogen not directly bound to the ^{15}N, and rapid exchange would be expected to decouple the nuclear spins.

Both the ^{19}F and ^{1}H nmr spectra of the other oxazolines listed in Table I were also consistent with the assigned structures. The ^{19}F spectra of all oxazolines containing CF_3 groups in the 2-position showed absorption in the range of 78-82 ppm higher field than fluorotrichloromethane (the spiro compounds prepared from perfluorocyclobutanone had the higher values), whereas the CF_3 groups in the 5-position were near 74 ppm. These observations are consistent with those made earlier that *gem*-trifluoromethyl groups flanked by N and/or O atoms consistently appear at higher field than those attached to only one such atom in otherwise similar situations (5).

Properties of Aminooxazolines.

Although the aminoimidazoline **2** was found to be a potent skeletal muscle relaxant (3), the same investigators found that the very closely related aminooxazoline **3a** was very much less active (6). A comparison of the chemical and physical properties of these two related compounds has led us to propose a theory to explain this difference in physiological activity.

Several similarities exist between **2** and **3a**. Even though both compounds contain a primary amino group, they are essentially neutral in aqueous systems and will not form salts with strong acids. Both compounds can be nitrated with a mixture of fuming nitric and fuming sulfuric acids to give corresponding nitramino derivatives. Also, both compounds will form anions when treated with sodium methoxide in dimethyl sulfoxide, and these anions can be alkylated as illustrated by the reaction of **3a** with sodium methoxide and then methyl iodide to give a mixture of the monomethyl (**8**) and the dimethyl (**9**) derivatives.



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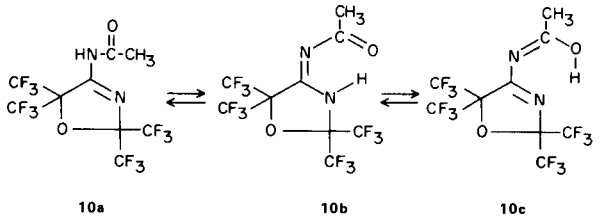
There is a difference, however, between the reactivity of **2** and **3a** towards electrophilic reagents. For example, **2** can be alkylated with methyl sulfate to give mono- and dimethyl derivatives (7), whereas **3a** will not react under the same or even more forcing conditions. This difference in reactivity is also apparent in acylation reactions. The aminoimidazoline **2** reacts easily with acetyl chloride at 51° (reflux) to give an acetyl derivative. No reaction occurs when **3a** is treated with acetyl chloride at reflux temperature; it is necessary to raise the temperature to 200° to effect acetylation.

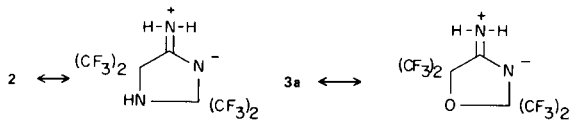
The acetyl derivative (**10**) is quite acidic, for it dissolves easily in aqueous sodium bicarbonate. Because of its acidity, establishing the tautomeric structure is difficult. It may exist in solution as an equilibrium mixture of all three possible tautomers (**10a**, **b** and **c**). The ultraviolet spectra in ethanol support this idea, since the molecular extinction coefficient for the λ max at 262 mμ changes on dilution, an indication that the tautomeric compositions may change with concentration.



10a 10b 10c

Another pronounced difference in properties between **2** and **3a** is their respective ability to form complexes with polar molecules. For example, **2** forms a stable, recrystallizable complex with dimethyl sulfoxide (2), but no such stable complex forms with **3a**. The complexing ability of these molecules may have an important bearing on their pharmacological activity. Aminoimidazoline **2** may block the transmission of nervous impulses by complexing with an active site necessary for such transmission. If so, **3a** would be expected to be much less active than 2, since it forms much weaker complexes. To obtain a quantitative measure of the relative complexing abilities of **2** and **3a**, the heats of complex formation of the two compounds with dimethyl sulfoxide were determined by standard calorimetry methods. Aminoimidazoline **2** with dimethyl sulfoxide gave a ΔH of about -6 Kcal/mole, whereas aminooxazoline **3a** gave a ΔH of only -1 Kcal/mole.

The ability of **2** to form complexes was previously suggested (2) to be due to the contribution of ionic resonance structure **11** to the over-all electronic structure of **2**. If this is true, then the corresponding ionic resonance structure **12** should be less important to the electronic structure of **3a**.

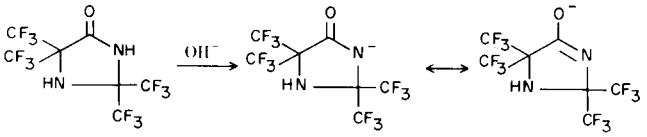


11 12

The low-temperature ^1H nmr spectrum of **3a** does indicate restricted rotation for the amino group, presumably because of the contribution of ionic resonance form **12**. The spectrum in acetone at $-52°$ shows distinct absorptions for each of the two hydrogens, separated by 0.77 ppm. The low-temperature spectrum of the ^{15}N-labeled sample further shows that each of the hydrogens is coupled to the ^{15}N by a slightly different amount. The lower field hydrogen has a J_{HN} of 92 cps, and the higher field hydrogen has a J_{HN} of 96 cps.

An attempt to obtain rotational energy barriers for the amino groups in **2** and **3a** from the ^1H nmr spectra, in order to assess the relative importance of ionic resonance forms of the two compounds, was unsuccessful because of experimental difficulties. It was found that the coalescence temperature of the signals due to the two hydrogens was extremely variable (from $-50°$ to $+17°$) and is apparently affected drastically by inadvertent trace amounts of water or other impurities in the solvent.

Since the only difference between **2** and **3a** is the identity of the atom(s) in the position transannular to the amidine function (NH for **2** and O for **3a**), the differences in reactivity and complexing ability of this function may be due to some transannular interaction. A similar type of interaction with an amide function is also indicated, for lactam **1**, with a pK_a of 2.22 in 40% ethanol, is considerably more acidic than lactam **13**, which has a pK_a of 6.25 in the same medium.



13 14a 14b

We propose that this transannular effect is due to interaction of the unshared pair of electrons on the transannular atom with the endocyclic π-bond in the 3-position of the ring, thus causing the π-bond to be destabilized. Such an interaction appears reasonable, since the transannular atom is held in very close proximity to the π-bond. Since the unshared pair of electrons on nitrogen are more available than those on oxygen, the rings containing the transannular nitrogen atom would tend to destabilize the endocyclic π-bond more than the rings containing oxygen. Thus, structures in which the π-bond is exocyclic, such as **11** and **14a**, should be favored for the imidazoline series of compounds more than the corresponding structures are favored for the oxazoline series. If this were true, it would explain the observed results, for the greater complexing ability of **2** as compared to **3a** could be due to the greater contribution of ionic resonance form **11** as compared to **12**, and the lower acidity of **13** as compared to **1** could be due to more localization of charge density on N as in ionic resonance from **14a**. The greater reactivity of **2**, as compared with **3a**, towards electrophiles could also be explained, since the transannular nitrogen would donate more electron density to the amidine function than would oxygen.

EXPERIMENTAL

Preparation of Fluorinated Aminooxazolines.

New oxazolines are listed in Table I. Typical preparative procedures are given below.

Method A. Reaction of Cyanohydrin Salt with Halogenated Acetone Imine. Preparation of 4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (3a).

Hexafluoroacetone (25 ml., at $-78°$, 0.25 mole) was slowly distilled into a stirred suspension of powdered sodium cyanide (12.25 g., 0.25 mole) in 200 ml. of acetonitrile. The temperature rose to 60° and was allowed to cool to 25°. Hexafluoroacetone imine (8) (27 ml., at $-10°$, 0.25 mole) was distilled into the reaction mixture, which was then stirred 3 days at room temperature. An equal volume of water was added and the mixture neutralized with 10% aqueous hydrochloric acid. The organic layer was separated and washed with water until a solid formed. The solid was collected on a filter, washed with water, dried, recrystallized from benzene, and sublimed at 130° (10 mm.) to give 33.0 g. of **3a** as colorless crystals: ^1H nmr, deuterioacetone, 2.34 τ (broad singlet); ^{19}F nmr, deuterioacetone, fluorotrichloromethane std., 73.7 ppm (m, 6F), 78.4 ppm (m, 6F).

Anal. Calcd. for $C_7H_2F_{12}N_2O$: C, 23.48; H, 0.56; N, 7.83; F, 63.67. Found: C, 23.43; H, 0.75; N, 7.90; F, 43.49.

Method B. Reaction of Cyanohydrin with Halogenated Acetone Imine in Presence of Piperidine Catalyst. Preparation of 4-Amino-2,2-bis(trifluoromethyl)-6,6,7,7,8,8-hexafluoro-3-aza-1-oxaspiro-[4.3]oct-3-ene.

Perfluorocyclobutanone (9) (72 ml., at 10°, 0.67 mole) was distilled into hydrogen cyanide (50 ml., 1.27 mole) containing 0.5 ml. of piperidine at $-10°$. The product was distilled to give 46.0 g. of perfluorocyclobutanone cyanohydrin as a colorless liquid which solidified on cooling, b.p. 63-65° (20 mm.).

Hexafluoroacetone imine (5 ml., at $-10°$, 0.03 mole) was distilled into a solution of hexafluorocyclobutanone cyanohydrin and 2 ml. (0.02 mole) of piperidine in 15 ml. of acetonitrile. The solution was stirred 4 days at room temperature. An equal volume of water was added and the solution neutralized with 10% hydrochloric acid. The crystals that formed were collected on a filter, washed with water and 10% sodium hydroxide, and sublimed (130°, 10 mm.) to give 6.51 g. (58%) of 4-amino-2,2-bis(trifluoromethyl)-6,6,7,7,8,8-hexafluoro-3-aza-1-oxaspiro[4.3]oct-3-ene: ^1H nmr deuterioacetone 2.52 τ (broad s); ^{19}F nmr, deuterioacetone,

fluorotrichloromethane std., 82.1 (m, 6F); 124.5 (m, 2F), 127.6 (m, 2F), 134.7 ppm (m, 2F).

Anal. Calcd. for $C_8H_2F_{12}N_2O$: C, 25.96; H, 0.54; N, 7.57; F, 61.61. Found: C, 26.14; H, 0.72; N, 6.76; F, 61.43.

4-Methylamino- and 4-Dimethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**8** and **9**).

Methyl iodide (16 g., 0.11 mole) was added dropwise to a solution of 17.9 g. (0.05 mole) of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**3a**) and 6.0 g. (0.11 mole) of sodium methoxide in 50 ml. of DMSO. The mixture was stirred overnight and poured into 200 ml. of water. The organic layer was extracted with ether, washed with water, dried (magnesium sulfate), and distilled to give two main fractions.

The lower boiling fraction, b.p. 88-90° (50 mm.), 6.2 g., solidified on cooling. Recrystallization from pentane gave 4.1 g. of **8** as colorless crystals, m.p. 59.5-60.5°; ir (potassium bromide) 5.96 μ; ^{1}H nmr deuterioacetone 2.25 τ (broad s, 1H) and 6.88 τ (d, J = 4.7 Hz; goes to singlet on addition of deuterium oxide, 3H); ^{19}F nmr deuterioacetone, fluorotrichloromethane std., 72.3 and 77.2 ppm (septets, J = 5.8, equal area).

Anal. Calcd. for $C_8H_4F_{12}N_2O$: C, 25.82; H, 1.08; F, 61.27; N, 7.53. Found: C, 25.58; H, 1.21; F, 61.23; N, 7.25.

The higher boiling fraction, b.p. 92-92.5° (50 mm.), 4.9 g., was purified by cooling to -10°, filtering off the solid, and redistilling the filtrate to give 2.7 g. of **9** as a colorless liquid: b.p. 92° (50 mm.); n_D^{25} 1.3460; ir (neat) 6.07 μ; ^{1}H nmr (neat) 6.84 τ (s); ^{19}F nmr (fluorotrichloromethane) 70.1 and 78.2 ppm (septets, 1:1).

Anal. Calcd. for $C_9H_6F_{12}N_2O$: C, 27.99; H, 1.57; F, 59.03; N, 7.26. Found: C, 27.72; H, 1.80; F, 59.23; N, 7.14.

4-Nitramino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline.

Red fuming nitric acid, 20 ml., was added rapidly to a stirred solution of 5.0 g. of **3a** in 30 ml. of 20% fuming sulfuric acid. The mixture was cooled and poured over crushed ice. The solid that formed was collected on a filter, washed with water, and redissolved in 5% sodium bicarbonate solution. The bicarbonate solution was filtered and the filtrate acidified (hydrochloric acid). The solid was recovered by filtration, washed with water, and sublimed (100°, 5 mm.) to give a colorless crystalline powder: m.p. 124-127°; uv, λ max (ethanol), 287 mμ (ϵ = 12,500); ^{19}F nmr, fluorotrichloromethane std., 2 septets at 73.2 and 77.3 ppm.

Anal. Calcd. for $C_7HF_{12}N_3O_3$: C, 20.86; H, 0.25; F, 56.56; N, 10.42. Found: C, 20.55; H, 0.18; F, 56.62; N, 10.34.

4-Acetylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-oxazoline (**10**).

A mixture of 6.3 g. of **3a** and 25 ml. of acetyl chloride was heated in a 80 ml. Hastelloy-lined bomb at 200° for 8 hours. The bomb was cooled and vented and the suspended solid collected on a filter and recrystallized from ethanol to give 3.1 g. of **10** as colorless needles: m.p. 189-190° (sealed cap.); ir (potassium bromide) 5.77 and 6.04 μ; ^{1}H nmr (deuterioacetone) 7.63 τ (s, 3H) and -0.3 τ (broad s, 1H); uv (ethanol) λ max 222 mμ and 262 mμ.

Anal. Calcd. for $C_9H_4F_{12}N_2O_2$: C, 27.01; H, 1.01; F, 56.98; N, 7.00. Found: C, 27.38; H, 1.30; F, 56.92; N, 6.94.

Hydrolysis of **3a**.

A solution of **3a** in 30 ml. of 90% sulfuric acid was slowly heated to 200° over 2 hours. The white sublimate that formed in the condenser was collected and dissolved in 5% sodium bicarbonate solution. The solution was filtered, and the filtrate acidified with concentrated hydrochloric acid. The solid that precipitated was collected on a filter, washed with water, and sublimed to give 0.5 g. of **1** as colorless crystals, m.p. 106-107°. The ir spectrum was identical with that of an authentic sample (1).

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