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PATENT SPECIFICATION

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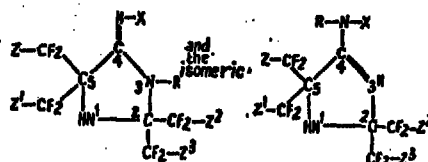
COMPLETE SPECIFICATION

Heterocyclic Compounds and methods of preparing the same

We, E. I. DU PONT DE NEMOURS AND COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, located at 10th and Market Streets, Wilmington, Delaware, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to, and has as its principal objects provision of, novel nitrogen heterocyclic compounds which have valuable biological activity and the preparation of the same.

The novel compounds of this invention are the 4-imino-2,2,5,5-tetrakis(poly-halomethyl)imidazolidines, their isomeric or tautomeric forms the 4-amino-2,2,5,5-tetrakis(polyhalomethyl)-3-imidazolines, and selected N-hydrocarbyl and N-acyl derivatives of the same. Formulae for these compounds are:



I. Imidazolidine Form II. Imidazoline Form

wherein:

(1) R may be hydrogen, hydrocarbyl, or hydrocarbyl substituted with up to 6 of the halogens fluorine, chlorine, and bromine and/or —OH, —NH₂, hydrocarbyloxy or hydrocarbylamino radicals, which latter two radicals may contain O or N in the hydrocarbon chain and/or be substituted by —OH, —NH₂, —COOH, —COOM, or halogen (halogen being as defined above and M being an alkali metal or an equivalent of an alkaline earth metal).

(2) X may be any of the possibilities defined for R



(R being as defined above); and

(3) Z, Z', Z'' and Z''' may be hydrogen or fluorine and either the same or different;

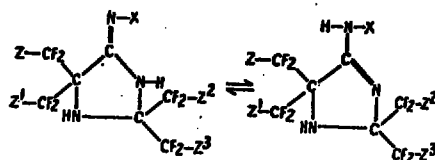
(4) With the proviso that R and X together contain no more than 30 carbon atoms.

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SEE ERRATA SLIP ATTACHED

The term "hydrocarbonyl" used herein means the radical of a hydrocarbon, and it includes alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, alkaryl and aralkyl radicals. The hydrocarbonylamino group referred to above may constitute a heterocyclic ring based on the nitrogen atom, while the O or N in a hydrocarbonyl chain may be the hetero-atom of a heterocyclic ring.

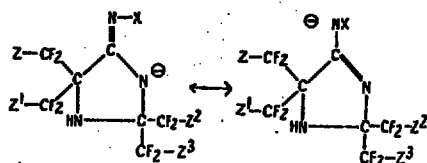
Compounds of the above structure in which R and/or X is H are tautomers, and exist in tautomeric equilibrium, especially in solution, as shown by the following formulas:



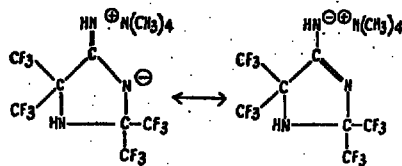
As would be expected from this tautomeric equilibrium involving a mobile proton, these compounds have marked acidic properties. For example, this hydrogen will exchange rapidly with deuterium when D_2O is added to an acetone solution of the compound, as evidenced by the disappearance of the NH absorption band in the nuclear magnetic resonance spectrum.

In the special case of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, in which both R and X are H, and all Z's are F, these two hydrogens exchange with each other so rapidly that only a single absorption band is observed at $25^\circ C$. from these protons in the n.m.r. spectrum; and they both exchange rapidly with D_2O .

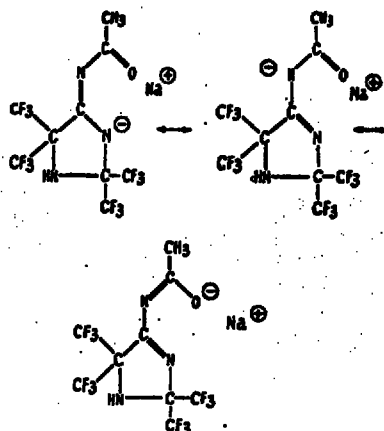
Since compounds of types I and II in which R is H exhibit acidic properties, they can form salts with bases. The salts from the two tautomers are identical, for their anions can be represented by the following resonance forms corresponding to the tautomeric forms of types I and II.



For example, 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine is a weak acid. It can be titrated with a strong base, such as tetramethylammonium hydroxide, in a non-aqueous solvent such as pyridine, to give a sharp end-point. The salt formed in this titration can be represented by the resonance structures:



4 - Acetylimino - 2,2,5,5 - tetrakis(trifluoromethyl)imidazolidine (R = H, X = CH_3CO- , and all Z's = F) is a stronger acid. It can be titrated in water with sodium hydroxide to give a salt that can be represented by the resonance structures:



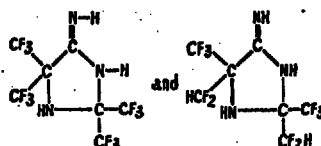
Compounds of the invention in which neither R nor X is H also exist as isomeric structures corresponding to the forms I and II. Either one or both types of these compounds can be prepared in a single reaction by causing a tautomeric mixture, in which R is H or R and X both are H, to react with an appropriate, for example hydrocarbylating or acylating, reagent. For example, a dimethyl derivative corresponding to type I (R and X=CH₃ and all Z's=F) and a dimethyl derivative corresponding to type II (R=X=CH₃ and all Z's=F) can be prepared in a single reaction by treating 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine with dimethyl sulfate.

Compounds of this invention in which R or X contain an amino moiety will form salts with acids such as hydrogen chloride and acetic acid, and will form quaternary ammonium salts with alkyl halides such as methyl iodide. Such salts are usually more water-soluble than the compounds from which they are derived but have the same general utilities. For the pharmacological purposes of the invention (see below), it will be understood that the acids or bases used to form salts are to be pharmacologically acceptable.

The compounds of this invention cause striking pharmacological effects therapeutically useful in the treatment of neurological and psychiatric disorders. Thus, they exert depressant effects upon the central nervous system, decreasing skeletal muscle tone, a desirable property for treatment of hypertonic or hyperkinetic motor disorders. This property is also useful in causing relaxation in general anesthesia.

Preferred compounds include those in which any alkyl substituent contains 1—4 carbon atoms; any aryl, aralkyl or alkaryl substituent contains 6—8 carbon atoms; and any hydrocarbyloxycarbonyl substituent contains 1—13 carbon atoms.

The compounds of the invention shown in the formulae first given can be prepared by processes the characteristic step of which is the reaction of the appropriate polyfluoroisopropylideneimine with an alkali metal cyanide. Upon heating, the following group of compounds is produced which are those of the formulae first given in which R and X are H as follows:

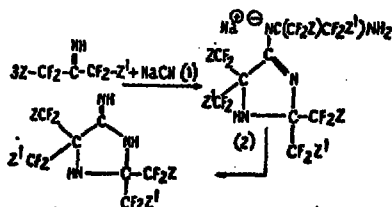


The compounds just mentioned are themselves preferred pharmacological agents of the invention and additionally serve as precursors for other of the compounds by chemical procedures of conventional character well understood by anyone skilled in the chemical arts.

The synthesis discussed generally above can be carried out as a two-step process including

- (1) a reaction between the polyfluoroalkylidenimine and the alkali metal cyanide, e.g., sodium or potassium cyanide, to form a polyfluoromethylethylamino-substituted intermediate followed by
- (2) heating of the intermediate to eliminate the polyfluoromethylethylamino sub-

stituent, preferably in an acid such as a mineral acid and most preferably, as illustrated hereinafter, in concentrated sulfuric acid. An equation for this process, in which Z's are as defined above, can be written (again disregarding isomerism) as:



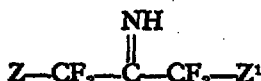
5 The polyfluoromethylethylamino-substituted intermediate can be isolated and is itself one of the compounds of the invention.

It will be understood that, if it is desired that more than two Z's be different in the reaction above, more than one imine must be employed in the reaction mixture with more than one resultant product. It will also be understood that, while the stoichiometry of the intermediate requires that three moles of the imine react with one of the inorganic cyanide, the proportions of the reactants in the reaction mixture are relatively unimportant other than to conserve materials. The order of mixing the reactants is not critical.

15 The above process is preferably carried out in an inert reaction medium such as dimethylformamide; dimethyl sulfoxide; liquid nitriles, e.g., acetonitrile and benzonitrile; glycol ethers, e.g., dimethyl ethers of ethylene and diethylene glycols.

The reaction is exothermic and the rate of addition of the imine to the alkali metal cyanide, or the cyanide to the imine, is adjusted so that the reaction temperature is preferably maintained in the range of $-40^{\circ}\text{C}.$ to $100^{\circ}\text{C}.$ Preferably the temperature is held in the lower portion of this operable range in order to minimize formation of by-products. The reaction mixture that is obtained at the completion of the addition of reactants is preferably acidified with a dilute aqueous solution of a mineral acid, e.g., 10% hydrochloric acid, to form, in the case where hexafluoroisopropylideneimine is used as the imine reactant, 4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethylamino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline. This intermediate is dissolved in concentrated sulfuric acid and heated for a few minutes, e.g., 10 minutes, at a temperature of about $100-150^{\circ}\text{C}.$ After cooling to $20^{\circ}\text{C}.$, the solution may be poured onto crushed ice whereupon solid 4-imino-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine is precipitated. This product can be isolated and purified by conventional means.

The imines of the formula



used as starting materials in the above-described process can be prepared in various ways. Halofluoroisopropylideneimine can be prepared as shown in United States Patent No. 3,226,439, and in J. Org. Chem. 30, 1398 (1965). The imines in which Z or Z', or both, are hydrogen, can be prepared by a modification of the method of Zeifman et al., Akad. nauk S.S.S.R. Doklady, 153, 1334 (1963), for preparing hexafluoroisopropylideneimine. The process for preparing pentafluoroisopropylideneimine involves first reacting pentafluoroacetone with phenyl isocyanate at about $200^{\circ}\text{C}.$ in the presence of a catalytic amount of a triarylphosphine oxide to form N-phenyl-pentafluoroisopropylideneimine, which is then treated with ammonia to give N-phenyl-2,2-diaminopentafluoropropane. This product, which need not be isolated or purified prior to the next and last step, is then reacted with phosphorus pentoxide, whereby it splits off aniline with formation of pentafluoroisopropylideneimine.

45 The compounds of the invention in which R and/or X is other than hydrogen can be prepared from those in which both R and X are hydrogen, or the alkali metal salts of these latter compounds, by treatment with conventional reagents, more especially hydrocarbylating, substituted hydrocarbylating or acylating agents. The resulting derivatives are also novel compounds which are useful for various purposes. The reaction can be carried out by contacting the imidazolidines ($\text{R}=\text{X}=\text{H}$), or the alkali metal salts of the imidazolidines, with the alkylating or acylating or other reagents, without solvent or in the presence of an inert solvent, at a temperature from

0° to 200°C., and isolation of the product by conventional means, such as distillation, recrystallization, or sublimation.

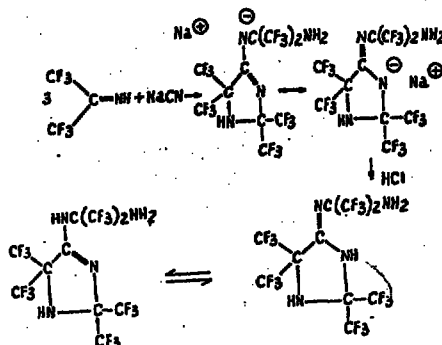
The hydrocarbylated derivatives are the compounds of this invention in which either R or R and X are hydrocarbyl groups or substituted hydrocarbyl groups. Suitable reagents include hydrocarbyl or substituted hydrocarbyl sulfates, *p*-toluenesulfonates, and halides. Other special alkylating reagents, such as formaldehyde or formaldehyde in combination with ammonia or amines (Mannich aminomethylating reagents), can be used to produce compounds in which R is hydroxymethyl, hydroxymethoxymethyl, or aminomethyl.

The acylated derivatives are the compounds of this invention in which X is acyl or substituted acyl. Suitable acylating reagents are acyl (or substituted acyl) halides and anhydrides and ketenes. In the special case in which the reagent oxalyl chloride is used, 4-isocyanato-2,2,5,5-tetrakis(polyfluoromethyl)-3-imidazolines are formed, and these isocyanates can be further reacted with alcohols to give carbamates. They can also be reduced to give 4-methylamino compounds.

This invention is illustrated in further detail by the following examples:

EXAMPLE 1

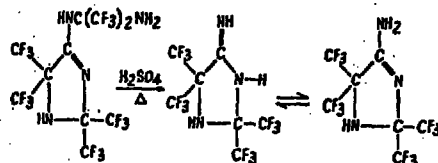
A. Preparation of 4-[1-Amino-2,2,2-trifluoro-1-(trifluoromethyl)ethylamino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline
 $R=H$; $X=-C(CF_3)_2NH_2$; All $Z's=F$



Hexafluoroisopropylidenimine, 20 ml. at -10°C . (ca. 30.8 g., 0.187 mole), was slowly distilled into a stirred suspension of 3.06 g. (0.0625 mole) of powdered sodium cyanide in 50 ml. of dimethyl sulfoxide. An exothermic reaction ensued. The rate of addition of the imine was adjusted so that the temperature of the reaction mixture did not rise above 65°C . At the end of the addition, about 20 minutes being required, the reaction mixture became homogeneous. The mixture was cooled to 20°C . and then poured into 500 ml. of water containing 100 ml. of 10% hydrochloric acid. The oil that formed was separated by decanting the aqueous phase. Fresh water (500 ml.) was added, and the oil and water were shaken vigorously together. The oil solidified. This solid was collected on a filter and pressed dry, and then dried in a vacuum desiccator over phosphorus pentoxide. There was obtained 24.1 g. (74% of theory) of 4-[1-amino-2,2,2-trifluoro-1-(trifluoromethyl)ethylamino]-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as a hydrophobic white solid, m.p. $45-46^\circ\text{C}$. A sample was recrystallized from pentane for analysis. The F^{19} n.m.r. spectrum in CDCl_3 showed two septets ($J=5.0$ c.p.s.) centred at 72.8 and 77.9 p.p.m. from trichlorofluoromethane used as an internal standard, and a singlet at 79.8 p.p.m., all of equal area. The proton n.m.r. spectrum in CDCl_3 showed two very broad singlets at 5.55 and 3.57 p.p.m. (each, area 1) and a broad singlet at 3.08 p.p.m. (area 2) from tetramethylsilane used as an internal standard. The infrared spectrum showed a band at 5.97μ .

Anal. Calcd. for $\text{C}_{10}\text{H}_4\text{F}_{18}\text{N}_4$: C, 23.00; H, 0.77; F, 65.49
 Found: C, 23.21; H, 0.91; F, 65.23

B. Preparation of 4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine
 $R = X = H$; All $Z's = F$



4 - [1 - Amino - 2,2,2 - trifluoro - 1 - (trifluoromethyl) - ethylamino] - 2,2,5,5 - tetrakis(trifluoromethyl) - 3 - imidazoline, 47.1 g., prepared as described in Part A above, was dissolved in 100 ml. of concentrated sulfuric acid, and the stirred solution was heated slowly to 150°C. and held at that temperature for 10 minutes. Frothing occurred during the heating period. The solution was then cooled to 20°C. and poured over 1 liter of crushed ice. The white solid that formed was collected on a filter after the ice had melted, and was washed with water. Recrystallization from alcohol-water (1:2) gave 31.5 g. (98% yield) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as long, colorless needles, m.p. 158—159°C.

EXAMPLE 2

Preparation of 4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R = X = H$; All $Z's = F$

This example illustrates the removal of the polyfluoromethylethylamino substituent from the intermediate, i.e., step 2 of the process, by heating the reaction mixture of the first step during distillation at atmospheric pressure to eliminate solvent.

Hexafluoroisopropylidenimine (25 g., 0.15 mole) was slowly distilled into a stirred suspension of 10 g. (0.2 mole) of sodium cyanide in 50 ml. of acetonitrile. An exothermic reaction ensued. The mixture was cooled to keep the temperature below 35°C. After the addition, the reaction mixture was stirred for 30 minutes at room temperature, and then 50 ml. of water was added. The pH of the solution was adjusted to 7 by the addition of a small quantity of hydrochloric acid. The organic layer was separated, washed twice with water and dried with anhydrous magnesium sulfate. The liquid was removed by distillation at atmospheric pressure, and the solid residue was recrystallized twice from benzene using decolorizing charcoal. There was obtained 4.1 g. (15% of theory) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as colorless needles, m.p. 159—160°C. The proton n.m.r. spectrum in dimethyl sulfoxide contained a broad singlet at +7.2 p.p.m. (area 2) and a sharp singlet at +6.06 p.p.m. (area 1). The F^{19} n.m.r. spectrum in acetone contained a pair of septets ($J = 4.7$ c.p.s.) at 71.5 and 76.5 p.p.m. for trichlorofluoromethane used as an internal standard. The infrared spectrum contained bands at 2.85, 2.9, 2.96, 3.04, 3.10, 3.16, 5.9, and 6.2 μ . The very strong band at 5.9 μ indicates the 4-imino tautomer to be present in major amount.

Anal. Calcd. for $C_7H_3F_{12}N_3$:

C, 23.55; H, 0.85; F, 63.85; N, 11.77

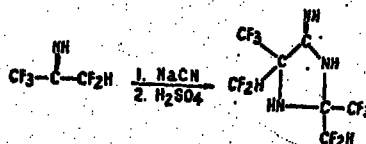
Found: C, 23.77; H, 1.35; F, 64.05; N, 12.05

The muscle-relaxant activity of this compound, 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, is demonstrated by the production of loss of the righting reflex in mice [Domino, E. F., et al., J. Pharmacol. Exptl. Therap., 105, 486—497 (1952)] and in producing abolition of muscular rigidity in decerebrate cats [Goodman, L., Bull. New England Med. Center 5, 97—100 (1943)]. The compound is 10 to 60 times as active as chlordiazepoxide, a drug widely used in the treatment of disorders of the skeletal muscle system. In addition, it has a therapeutic ratio of 12 in the mouse-relaxant test in comparison with that of chlordiazepoxide which has a therapeutic ratio of 6.5.

EXAMPLE 3

4-Imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)imidazolidine

$R = X = H$; $Z = Z' = F$; $Z'' = Z''' = H$



A solution of 24.1 g. (0.163 mole) of pentafluoroisopropylidenimine (prepared as described below) in 50 ml. of dimethylformamide was cooled to 0°C. and 4.9 g. (0.1 mole) of powdered sodium cyanide was added portionwise over a period of 30 min. Cooling was maintained so that the temperature did not rise above 5°C. The reaction mixture was stirred for 2 hours at 25°C. and then poured into 200 ml. of 10% hydrochloric acid. The oil that separated, i.e., crude 4 - [1 - amino - 2,2 - difluoro - 1 - (trifluoromethyl)ethylamino] - 2,5 - bis(difluoromethyl) - 2,5 - bis(trifluoromethyl) - 3 - imidazoline, was washed with 200 ml. of water, and then dissolved in 25 ml. of 20% fuming sulfuric acid. The sulfuric acid solution was heated to 150°C., cooled, and poured over 25 g. of ice. The solid that formed was collected on a filter and washed with water. Sublimation at 100°C. (10 mm.) gave 2.9 g. of a white crystalline powder, m.p. 118—119.5°C. (sealed cap.; Product A).

The filtrate was diluted further with 200 ml. of water and made slightly basic with 50% aqueous potassium hydroxide. The precipitate that formed was collected on a filter, washed with water, dried in air, and sublimed at 100°C (10 mm). There was obtained 5.79 g. of 4-imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-imidazolidine as a white crystalline powder, m.p. 142—144°C. (sealed cap.; Product B). The F^{19} n.m.r. of product B in acetone indicated that it was a mixture of two isomers, with one predominating. The CF_3 region showed a complex multiplet at +72.8 p.p.m. (3F) and complex multiplets in about a 1:2 ratio at 77.1 and 77.7 p.p.m. (both together, 3F); the CF_2H region showed two doublets ($J=54$ c.p.s.) split further into complex multiplets centered at +127.0 and +131.0 p.p.m. The H^1 n.m.r. showed two triplets ($J=54$ c.p.s.) with shoulders centred at τ 3.56 and τ 3.98 (1H each); a broad absorption at τ 5.12 (1H) and a very broad absorption at τ 3.0 (2H). The infrared absorption showed a band at 5.91μ for $C=N$.

Anal. Calcd. for $C_7H_5F_{10}N_3$:

C, 26.18; H, 1.57; F, 59.17; N, 13.08

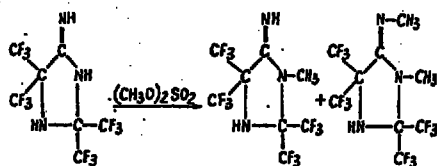
Found: C, 26.49; H, 1.45; F, 59.15; N, 12.92

The pentafluoroisopropylidenimine starting material can be prepared by reacting phenyl isocyanate with pentafluoroacetone in the presence of triphenylphosphine oxide at 200°C. to give N-phenylpentafluoroisopropylidenimine. This product is first reacted with ammonia and then with phosphorus pentoxide to produce the desired pentafluoroisopropylidenimine.

EXAMPLE 4

3-Methyl- and 3-Methyl-4-methylimino Derivatives of 4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R = -CH_3$; $X = H$ and $-CH_3$; All Z's = F



A solution of 10.0 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 20 ml. of dimethyl sulfate was heated quickly to boiling (ca. 188°C). Water, 50 ml., was added dropwise to the hot reaction mixture to decompose the excess dimethyl sulfate. The resulting solution was then cooled and neutralized with about 135 ml. of 10% aqueous sodium hydroxide, and the white solid that separated was collected on a filter, washed thoroughly with water, and dried in air. There was obtained 9.42 g. of a crude mixture of methylated derivatives. Gas chromatographic analysis in a column packed with firebrick impregnated with the petroleum grease known under the Trade Mark "Apiezon" L at 95°C. showed the mixture consisted of 73% of the dimethyl derivative (second eluted component) and 23% of the monomethyl derivative (first eluted component).

The two compounds were separated by fractional recrystallization from pentane. The progress of the recrystallizations was followed by gas chromatography, and each component was recrystallized until it was more than 99% pure.

Pure 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was obtained as the least soluble component (the original 23% component) in the form of colorless needles, m.p. 121—122°C. (sealed cap.). The infra-red spectrum showed a band at 5.95μ for $C=N$. The F^{19} n.m.r. in acetone showed a septet ($J=4.6$ c.p.s.) centered

at 73.6 p.p.m. and a multiplet at 75.4 p.p.m. from CCl_3F used as an internal standard. The H^1 n.m.r. in $(\text{CD}_3)_2\text{CO}$ showed a septet ($J_{\text{HF}} = 0.85$ c.p.s.) at 3.12 p.p.m. (area 3) and two broad absorptions at 8.1 and 5.95 p.p.m. (area, 1 each).

Anal. Calcd. for $\text{C}_8\text{H}_5\text{F}_{12}\text{N}_3$:

C, 25.89; H, 1.36; F, 61.43; N, 11.32

Found: C, 25.92; H, 1.54; F, 60.73; N, 11.92

Pure 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was obtained as the most soluble component (the original 73% component) in the form of a white crystalline powder, m.p. 48–49°C. The infrared spectrum showed a band at 5.92μ for $\text{C}=\text{N}$. The F^{19} n.m.r. spectrum in acetone showed a pair of septets ($J = 4.6$ c.p.s.) at 73.6 and 75.4 p.p.m. from CCl_3F used as an internal reference. The H^1 n.m.r. spectrum in $(\text{CD}_3)_2\text{CO}$ showed singlets at 3.33 and 3.02 p.p.m. (area 3 each) and a broad absorption at 6.25 p.p.m. (area 1) from $(\text{CH}_3)_4\text{Si}$ used as an internal reference.

Anal. Calcd. for $\text{C}_9\text{H}_7\text{F}_{12}\text{N}_3$:

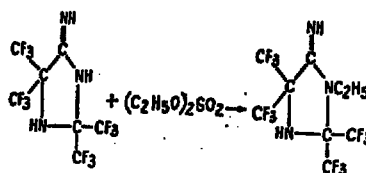
C, 28.06; H, 1.83; F, 59.20; N, 10.91

Found: C, 28.30; H, 1.89; F, 58.51; N, 10.65

EXAMPLE 5

3-Ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R = -\text{C}_2\text{H}_5$; $X = \text{H}$; All Z 's = F



A mixture of 5.0 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 10 ml. of diethyl sulfate was heated to boiling (ca. 200°C.) for 5 minutes, and then water was cautiously added to the hot reaction mixture to decompose the excess diethyl sulfate. Activated charcoal, 1.0 g., was added, and the mixture filtered. The filtrate was neutralized with 10% aqueous sodium hydroxide, and the solid that precipitated was collected on a filter and recrystallized from pentane. There was obtained 2.48 g. of 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as colorless needles, m.p. 113–114°C. (sealed cap.). The infrared spectrum contained a band at 5.96μ . The F^{19} n.m.r. spectrum in acetone showed two septets ($J = 4.6$ c.p.s.) centered at 73.7 and 75.4 p.p.m. from CCl_3F used as an internal standard. The H^1 n.m.r. showed two broad absorptions at 6.30 and 7.75 p.p.m. (area 1 each), a quartet ($J = 7$ c.p.s.) centered at 3.54 p.p.m. (area 2), and a triplet ($J = 7$ c.p.s.) centered at 1.15 p.p.m. (area 3) from $(\text{CH}_3)_4\text{Si}$ used as an internal reference.

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{F}_{12}\text{N}_3$:

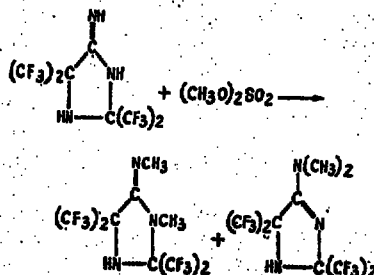
C, 28.06; H, 1.83; F, 59.20; N, 10.91

Found: C, 28.40; H, 2.16; F, 58.96; N, 11.16

EXAMPLE 6

4-Dimethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R = X = -\text{CH}_3$; All Z 's = F



A 10.0 gram sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 30 ml. of dimethyl sulfate (excess) were heated together for 8 hours at 200°C. in an 80-ml. autoclave lined with the corrosion-resistant alloy known under the Trade Mark Hastelloy. The bomb was cooled to 0°C. and vented. Excess dimethyl sulfate in the recovered dark residue (44 g.) was decomposed at its boiling point by adding 10 ml. of water to it dropwise over 0.5 hour under reflux. The mixture was cooled and neutralized with dilute sodium hydroxide solution. Ether extraction followed by washing (water), drying (magnesium sulfate), and evaporation of the ether extracts led to a white semisolid. The semisolid was dissolved in hot ether-pentane, cooled and filtered. The filtrate was subjected to preparative gas chromatographic analysis, and the two major components excluding solvents were isolated from the effluent gases by trapping with liquid nitrogen. The compound eluted first on a silicone column was 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (about 1 g. isolated). The compound eluted second (0.8 g. isolated), m.p. 30–33°C., was shown to be 4-dimethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline, on the basis of the following: H^1 n.m.r., sharp $(CH_3)_2N$ at 3.19 p.p.m. and NH at 6.05 p.p.m.; F^{19} n.m.r., pair of septets ($J=4$ c.p.s.) at +69.4 and +7.78 p.p.m. from internal $CFCl_3$ at 56.4 Mc.; IR, in the ring $C=N$ at 6.12 μ and sharp NH at 2.88 μ .

Anal. Calcd. for $C_9H_7N_3F_{12}$ (385.17):

C, 28.06; H, 1.83; F, 59.20; N, 10.91

Found: C, 28.51; H, 2.28; F, 59.33; N, 10.85

EXAMPLE 7

A. 3-Ethyl-4-ethylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and

B. 4-Ethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

A. $R = -C_2H_5$; $X = -C_2H_5$; All $Z's = F$

B. $R = H$; $X = -C_2H_5$; All $Z's = F$

A solution of 20.0 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 50 ml. of diethyl sulfate was heated at reflux for 75 min., and then water (20 ml.) was cautiously added to the hot reaction mixture to decompose any excess diethyl sulfate. The black reaction mixture was diluted with 300 ml. of water and neutralized with 6N sodium hydroxide. The organic phase was separated by steam distillation (total volume 100 ml.) followed by ether extraction of the distillate. Concentration gave 23.8 g. of a mixture of solid and oil. The entire sample was retreated with 40 ml. of diethyl sulfate at reflux and isolated as above to give 21.5 g. of an oil. Gas chromatographic analysis showed the oil to consist of 56% of a material with retention time of 10.9 min., 33% of a material with retention time of 12.6 min., 7% of 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 2% of unreacted starting material.

Preparative gas chromatography afforded pure samples of the two major components. The compound (A) eluted first was 3-ethyl-4-ethylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, isolated as an oil, n_D^{25} 1.3624. Distillation through a short path still afforded an analytical sample: H^1 n.m.r. 6.7 τ — wt. 5, multiplet of roughly two quartets with another overlying peak; and 9.0 τ — wt. 6, two overlapping triplets centering at 9.01 ($J=7.5$ c/s) and 9.03 ($J=6.0$ c/s). In $CdCl_2$, addition of trifluoroacetic acid and deuterium (two phase) changed the 6.7 peak to clean quartet (wt. 4) and 9.0 peak to a triplet (wt. 6). The mass spectrum showed a parent peak at m/e 413.

IR: 3480 (NH) and 1705 cm^{-1} ($C=N$)

Anal. Calcd. for $C_{11}H_{11}F_{12}N_3$:

C, 32.0; H, 2.7; F, 55.2; N, 10.2

Found: C, 32.0; H, 2.8; F, 55.7; N, 10.3

55.7

The compound eluted second (B) was 4-ethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline isolated as an oil, n_D^{25} 1.3541. An analytical sample was obtained by distillation through a short path still: H^1 n.m.r. 5.12 τ — wt. 1, broad triplet; 6.6 τ — wt. 3, multiplet, appearing to be roughly a quartet split into doublets with an overlapping triplet; and 8.98 τ — wt. 3, triplet ($J=7.2$ c/s). In $CDCl_3$, addition of trifluoroacetic acid and deuterium oxide caused the spectrum to simplify to a quartet (wt. 2) at 6.6 τ and a triplet (wt. 3) at 8.9 τ along with a sharp exchange

DOH peak. The mass spectrum showed a parent peak at m/e 385 and the base peak at m/e 316 (parent $-CF_3^+$).

Anal. Calcd. for $C_9H_8F_{12}N_3$:

C, 28.1; H, 1.8; F, 59.2; N, 10.9

Found: C, 28.0; H, 2.2; F, 58.7; N, 11.2
59.0

EXAMPLE 8

3-Ethyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R = -C_2H_5$; $X = -CH_3$; All Z 's = F

A solution of 5.0 g. of 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine in 5 ml. of dimethyl sulfate was heated to reflux for 2 min. and treated with water (1 ml.) while still hot to decompose the excess dimethyl sulfate. An additional 15 ml. of water was added and the mixture was neutralized with 6N sodium hydroxide. The organic phase was separated by ether extraction (3×10 ml.) and concentration. The resulting yellow oil (5.3 g.) was separated into two major compounds by preparative gas chromatography. The major component (76%) was 3-ethyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, isolated as an oil. H^1 n.m.r. 6.6–6.9 τ — wt. 6, multiplet appearing to consist of a quartet ($J=7$ c/s) at 6.68 τ sharp singlet at 6.88 τ and a broad NH centered at 6.62 τ ; and 9.03 τ — wt. 3, triplet ($J=7$ c/s). The mass spectrum contained a parent peak at m/e 399 with a base peak at m/e 302 (parent $-CF_3$ and $C_2H_4^+$).

IR: 3520 (NH) and 1710 cm^{-1} ($C=N$)

Anal. Calcd. for $C_{10}H_9F_{12}N_3$:

C, 30.1; H, 2.3; F, 57.1; N, 10.5

Found: C, 30.8; H, 2.5; F, 57.0; N, 10.6
30.7 2.6 57.1 10.2

The second major component (15%) was shown to be identical with 4-dimethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline.

EXAMPLE 9

4-Ethylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R = -CH_3$; $X = -C_2H_5$; All Z 's = F

A solution of 5.0 g. of 3-methyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine in 12.5 ml. of diethyl sulfate was heated to reflux for 15 min. The black mixture was cautiously treated with 5 ml. of water while still hot to decompose the excess diethyl sulfate. An additional 30 ml. of water was added and the mixture neutralized with 6N sodium hydroxide. A drop of silicone antifoam was added and the mixture distilled until 20 ml. of distillate was collected. The organic phase (4.2 ml.) was extracted into ether (20 ml. and 2×10 ml.). The ether extracts were dried over magnesium sulfate and concentrated to give 5.5 g. of an oil. The crude mixture was subjected to preparative gas chromatography (butanediol succinate at $75^\circ C$.) to give an oil which was identical with 4-ethylimino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline, and 1.81 g. of an oil which was shown to be 4-ethylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, n_D 1.3615. This material had an I.R. absorption spectrum very similar to that of its 3-ethyl-4-methylimino isomer. However, their mass spectra were very different with the 4-ethylimino-3-methyl isomer containing the parent peak at m/e 399 and its base peak at m/e 384 (parent $-CH_3^+$).

Anal. Calcd. for $C_{10}H_9F_{12}N_3$:

C, 30.1; H, 2.3; F, 57.1; N, 10.5

Found: C, 30.5; H, 2.5; F, 57.0; N, 10.3
30.8 2.6 57.0

When the procedures of Examples 4–9 are repeated with the dimethyl and diethyl sulfates of those examples replaced by appropriate dialkyl sulfates or alkyl *p*-toluenesulfonates in which the alkyl groups have up to 15 carbon atoms, the following alkyl derivatives of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidines (or their tautomers) can be obtained:

3-Butyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;

4-Dioctylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline;

3-Decyl-4-decylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine; and

3-Dodecyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

Likewise, when the procedures of Examples 4–9 are repeated with the particular 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidines of those examples replaced by

appropriate imidazolidines having difluoromethyl groups, in place of the trifluoromethyl groups, and similar alkylating agents are used, the following derivatives can be obtained:

4-n-Propylamino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline;

3-Butyl-4-imino-2,2,5,5-tetrakis(difluoromethyl)imidazolidine; and

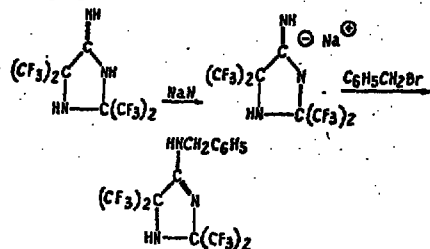
4-n-Hexyl-2,2,5,5-tetrakis(difluoromethyl)imidazolidine.

The alkylation of the alkali metal salts of 4-imino-2,2,5,5-tetrakis(polyfluoro-alkyl)imidazolidines with halide alkylating agents is illustrated in Examples 10—13.

EXAMPLE 10

4-Benzylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R = H$; $X = -CH_2C_6H_5$; All $Z's = F$



A 7 gram sample (0.02 mole) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine dissolved in 10 ml. of 1,2-dimethoxyethane was added at $<10^\circ\text{C}$. to 1 g. of 54% sodium hydride-mineral oil (0.02 mole) in 50 ml. of 1,2-dimethoxyethane. The stirred suspension was refluxed for 2 hr., cooled, and 4.0 g. (0.023 mole) of benzyl bromide was added at $<10^\circ\text{C}$. The mixture was heated at reflux for 22 hr. (yellow precipitate), cooled, and filtered to remove the sodium bromide. Distillation of the filtrate through a spinning band column gave 6.3 g. (70%) of 4-benzylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as a colorless liquid, b.p. 120°C . (10 mm.). The H^1 n.m.r. showed NH at τ 2.35 and τ 3.85, aromatic $-H$ at 2.68 and a doublet ($J=6$) for a $-CH_2-$ split by NH. The F^{19} n.m.r. showed a pair of septets ($J=5$) at 72.7 and 78.1 p.p.m. from $CFCl_3$. The mass spectrum showed a parent ion at m/e 447 which was 42% of the base peak at m/e 91 ($CH_2C_6H_5^+$).

Anal. Calcd. for $C_{14}H_9N_3F_{12}$:

C, 37.60; H, 2.03; F, 51.10; N, 9.40

Found: C, 37.59; H, 2.13; F, 50.87; N, 9.42

EXAMPLE 11

4-(Allylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R = H$; $X = -CH_2CH=CH_2$; All $Z's = F$

This compound, b.p. 87°C . (25 mm.), was prepared by a procedure similar to that of Example 10, except that 3.0 g. of 3-bromopropene was substituted for the benzyl bromide. The H^1 n.m.r. spectrum shows a complex absorption at τ 3.7—5.1 for $-CH=CH_2$ and one NH, a three-peak absorption at τ 5.9 for a CH_2 group split by NH and $-CH=$ and an NH at τ 6.4. The F^{19} n.m.r. spectrum shows a pair of septets at 72.8 and 78.0 p.p.m. from $CFCl_3$. The mass spectrum shows a parent ion (43%) at m/e 397 with the base peak at m/e 41 ($CH_2=CHCH_2^+$).

Anal. Calcd. for $C_{10}H_7N_3F_{12}$:

C, 30.24; H, 1.78; F, 57.40; N, 10.58

Found: C, 30.19; H, 2.16; F, 56.87; N, 10.42

EXAMPLE 12

4-Methylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R = H$; $X = -CH_3$; All $Z's = F$

A. This compound, along with other alkylated products, was isolated in 40% yield from a reaction conducted according to the procedure described for Example 10, except that 3.5 g. of methyl iodide was substituted for the benzyl bromide.

B. This material was also prepared by reduction of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline. To 0.70 g. (0.0184 mole) of lithium aluminium hydride in 100 ml. of ether was added 6.15 g. (0.0159 mole) of the isocyanate in 20 ml. of ether dropwise at $<10^\circ\text{C}$. After stirring at 25°C . for 24 hr., the mixture was decomposed with 200 ml. of 5% hydrochloric acid at $<10^\circ\text{C}$. The layers were separated and the aqueous layer was extracted with ether. The combined ether layers

were washed with water and dried over magnesium sulfate. The ether was removed by distillation and the residue was distilled at reduced pressure to give 2.3 g. (38%) of 4-methylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as a colorless liquid, b.p. 75°C. (10 mm.). The H^1 n.m.r. spectrum showed a doublet ($J=5.0$) at τ 6.90 for CH_3 split by NH and singlets at τ 5.05 and 6.50 for NH absorption. The mass spectrum showed its base peak at m/e 302 (parent $-CF_3$) and was consistent with the structure.

Anal. Calcd. for $C_8H_5F_{12}N_3$:

C, 25.89; H, 1.36; N, 11.32; F, 61.43

Found: C, 25.88; H, 1.51; N, 11.16; F, 60.89

EXAMPLE 13

4-Dimethylaminoethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R=H$; $X=-CH_2CH_2N(CH_3)_2$; All $Z's=F$

The sodium salt of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline was prepared as described in Example 10. Another equivalent (1 g.) of 54% sodium hydride-mineral oil and 4.85 g. of β -dimethylaminoethyl bromide hydrobromide were added successively at $<10^\circ C$. The mixture was refluxed for 24 hours, filtered, and the filtrate was distilled to give 5.0 g. (58%) of 4-dimethylaminoethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as a colorless liquid, b.p. 80–85°C. (7 mm.), that solidified to a white solid, m.p. 47–53°C. upon standing. A sample purified through the hydrochloride had m.p. 58–61°C. The H^1 n.m.r. of the free base showed NH bands at τ 3.4 and 3.9, triplets at 6.5 ($J=6$, split further) and at τ 7.46 for the NCH_2CH_2N group and a singlet at τ 7.78 for the $N(CH_3)_2$ group. The F^{19} n.m.r. spectrum showed a pair of septets ($J=5$) at 75.5 and 78.6 p.p.m. from $CFCl_3$. The mass spectrum showed a parent peak at m/e 428 with a base peak at m/e 58 $[(CH_3)_2NCH_2^+]$.

Anal. Calcd. for $C_{11}H_{12}N_4F_{12}$:

C, 30.85; H, 2.83; F, 53.24; N, 13.08

Found: C, 30.37; H, 2.63; F, 53.40; N, 13.94

When the procedures of Examples 10–13 are repeated with the alkylating agents of these examples replaced by appropriate hydrocarbyl or substituted-hydrocarbyl halides, the following derivatives of 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)-imidazolidines (or their tautomers) can be obtained:

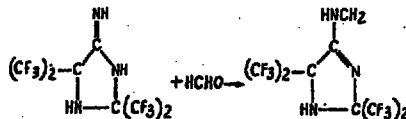
- 4-Propargylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline;
- 4-Cyclohexylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline;
- 4-(2-Chloroethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline;
- 4-(2-Methoxyethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline; and
- 4-(2-Cyclohexenylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline.

The alkylation of the parent compounds with formaldehyde to form hydroxymethyl and hydroxymethoxymethyl derivatives is illustrated by Examples 14 and 15.

EXAMPLE 14

4-Hydroxymethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline

$R=H$; $X=-CH_2OH$; All $Z's=F$



A mixture of 10 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 50 ml. of 37% aqueous formaldehyde was heated to boiling. The resulting clear solution was cooled to $0^\circ C$., diluted with 200 ml. of cold water, and made strongly basic with 100 ml. of 10% sodium hydroxide. The white precipitate that formed was collected on a filter and recrystallized from ether-pentane (10–90%). There was obtained 6.1 g. of 4-hydroxymethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as a white crystalline powder, m.p. 90–92°C. The infrared spectrum showed a band at 6.00μ for $C=N$ and a strong band at 6.44μ for NH bending. The F^{19} n.m.r. spectrum in acetone showed two septets ($J=4.8$) centered at 72.1 and 77.1 p.p.m. from $CFCl_3$. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a very broad signal at τ 2.3 (NH), a singlet at τ 3.9 (NH), and a doublet ($J=5.4$) superimposed on a broader signal (3H) at τ 4.97 for CH_2OH .

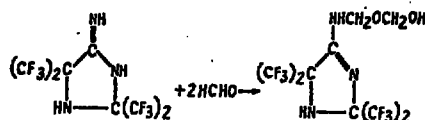
Anal. Calcd. for $C_8H_5F_{12}N_3O$:

C, 24.82; H, 1.31; F, 58.89; N, 10.86

Found: C, 25.37; H, 1.47; F, 58.57; N, 11.25

EXAMPLE 15

4-Hydroxymethoxymethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline
 $R=H$; $X=-CH_2OCH_2OH$; All $Z's=F$



A 10 gram sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was dissolved in 50 ml. of boiling 37% aqueous formaldehyde. The resulting solution was cooled and diluted with 100 ml. of water. The oil that separated was washed with water several times until it solidified. Recrystallization of the solid from ether-pentane gave 8.7 g. of 4-(hydroxymethoxymethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as colorless crystals, m.p. 106—108°C. The infrared spectrum showed a band at 6.00 μ for $C=N$ and a strong band at 6.44 μ for NH bending. The F^{19} n.m.r. spectrum in acetone showed two septets ($J=4.8$) centered at 72.3 and 77.2 p.p.m. from $CFCl_3$. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad signal at τ 2.13 (NH), a singlet at τ 3.72 (NH), a triplet ($J=7.5$) at τ 4.57 (OH), a doublet ($J=6$) at τ 4.92 (NCH_2O), and a doublet ($J=7.5$) at τ 5.15 (OCH_2O).

Anal. Calcd. for $C_{10}H_7F_{12}N_3O_2$:

C, 25.91; H, 1.69; F, 54.65; N, 10.07

Found: C, 25.88; H, 1.51; F, 54.56; N, 9.89

When the procedures of Examples 14 and 15 are repeated with 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidines having difluoromethyl groups substituted for the trifluoromethyl groups of the imidazolidines of those examples, the following compounds can be obtained:

4-Hydroxymethylamino-2,2,5,5-tetrakis(difluoromethyl)-3-imidazoline;

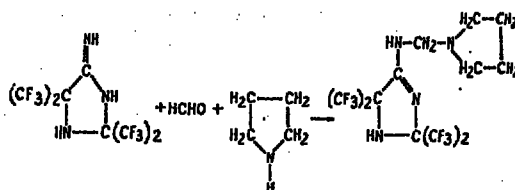
4-Hydroxymethylamino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline, and

4-(Hydroxymethoxymethylamino)-2,2,5,5-tetrakis(difluoromethyl)-3-imidazoline.

The dialkylaminomethyl derivatives of the parent compounds (i.e., dialkylaminomethyl derivatives of compounds where X and R in the general formula are H) can be prepared by condensing 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidines with formaldehyde and ammonia, a primary or a secondary amine, by the well-known Mannich reaction. These reactions can be accomplished by simply warming a mixture containing the 4-iminoimidazolidine, the amine, and formaldehyde (or a formaldehyde precursor such as paraformaldehyde) in water or an alcohol solvent such as ethanol or isoamyl alcohol. This procedure is illustrated in Examples 16, 18, 19, 20, and 23. The preparation of salts of these dialkylamino derivatives with inorganic acids and with alkyl halides is illustrated in Examples 17, 21, and 22.

EXAMPLE 16

4-(N-Pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline
 $R=H$; $X=N$ -pyrrolidylmethyl; All $Z's=F$



Pyrrolidine, 10 ml., was added to a hot (90°C) solution of 10 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 50 ml. of 37% formaldehyde (aqueous solution). The resulting reaction mixture was cooled, and the solid that precipitated was collected on a filter, washed with water, and dried. Recrystallization from pentane gave 9.6 g. of 4-(pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as colorless needles, m.p. 127—128°C. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad signal at τ 2.73 (NH), a broad singlet at τ 3.90 (NH), a singlet at τ 5.45 ($N-CH_2-N$) and multiplets at τ 7.3 (4H) and τ 8.3 (4H). The

F^{19} spectrum showed two septets ($J = 4.8$) centered at 71.0 and 77.2 p.p.m. from $CFCl_3$.

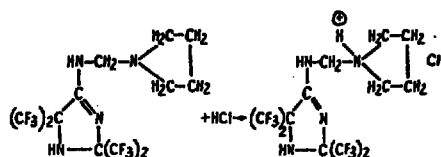
Anal. Calcd. for $C_{12}H_{12}F_{12}N_4$:

C, 32.74; H, 2.75; F, 51.79; N, 12.73

Found: C, 32.58; H, 3.02; F, 52.30; N, 12.75

EXAMPLE 17

4-(N-Pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Hydrochloride

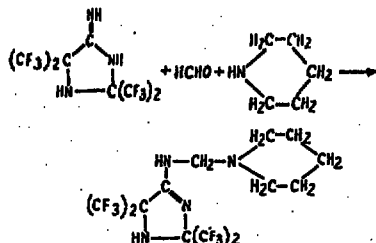


A solution of 3.0 g. of 4-(N-pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline in 50 ml. of ether was saturated with dry hydrogen chloride gas. The white precipitate that formed was collected on a filter and washed with ether. There was obtained 3.1 g. of the hydrochloride as a white crystalline powder, m.p. 123—126°C.

Anal. Calcd. for $C_{12}H_{13}F_{12}N_4Cl$: Cl, 7.44
Found: Cl, 7.00

EXAMPLE 18

4-(N-Piperidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline $R = H$; $X = N$ -piperidylmethyl; All Z 's = F



Piperidine, 10 ml., was added to a hot (90°C.) solution of 10 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 50 ml. of 37% formaldehyde (aqueous solution). The reaction mixture was cooled and 100 ml. of water was added. The oil that separated solidified upon standing overnight. The solid was collected on a filter, washed with water, and recrystallized from pentane. There was obtained 8.9 g. of 4-(N-piperidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as colorless prisms, m.p. 87—88°C. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad signal at τ 2.83 (NH), a broad singlet at τ 3.92, a doublet ($J = 6$) at τ 5.57 (N—CH₂—N), and multiplets at τ 7.4 (4H) and τ 8.55 (6H). The F^{19} n.m.r. spectrum showed two septets ($J = 4.8$) centered at 71.8 and 77.1 p.p.m. from $CFCl_3$.

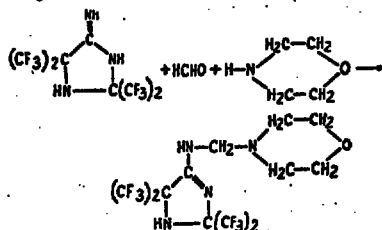
Anal. Calcd. for $C_{12}H_{14}F_{12}N_4$:

C, 34.37; H, 3.11; F, 50.19; N, 12.33

Found: C, 34.00; H, 3.31; F, 50.01; N, 12.34

EXAMPLE 19

4-(N-Morpholinylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline
 $R=H$; $X=N$ -morpholinylmethyl; All Z 's = F



Morpholine, 10 ml., was added to a solution prepared by dissolving 10 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 50 ml. of 37% formaldehyde (aqueous solution). Water, 100 ml., was added and the mixture was cooled. The oil that separated solidified after cooling for 20 hours. The solid was collected on a filter, washed with water, and recrystallized from pentane-ether. There was obtained 3.3 g. of 4-(N-morpholinylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as colorless crystals, m.p. 139—140°C. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad signal at τ 2.57 (NH), a singlet at τ 3.80 (NH), a doublet ($J=6$) at τ 5.54 (NCH₂N), and multiplets at τ 6.38 (4H) and τ 7.38 (4H). The F^{19} n.m.r. spectrum showed two septets ($J=4.8$) at 71.0 and 77.1 p.p.m. from $CFCl_3$.

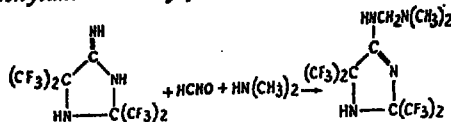
Anal. Calcd. for $C_{12}H_{12}F_{12}N_4O$:

C, 31.59; H, 2.65; F, 49.97; N, 12.28

Found: C, 31.22; H, 2.74; F, 49.89; N, 12.12

EXAMPLE 20

4-Dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline
 $R=H$; $X=dimethylaminomethyl$; All Z 's = F



A 10 g. sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was dissolved in 50 ml. of boiling 37% formaldehyde (aqueous solution). The solution was stirred and cooled to 25°C., and 10 ml. of dimethylamine was distilled into the solution over a period of 10 min. The solid that formed was collected on a filter and washed with water. Recrystallization from pentane gave 9.3 g. of 4-dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline as colorless needles, m.p. 113—114°C. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad absorption at τ 2.76 (NH), a singlet at τ 3.87 (NH), a doublet ($J=5$) at τ 5.60 (NCH₂N), and a singlet at τ 7.70 (2CH₃). The F^{19} n.m.r. spectrum showed two septets ($J=4.8$) at 72.2 and 77.2 p.p.m. from $CFCl_3$.

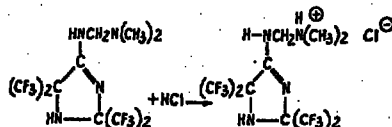
Anal. Calcd. for $C_{16}H_{16}F_{12}N_4$:

C, 29.00; H, 2.44; F, 55.04; N, 13.52

Found: C, 29.04; H, 2.28; F, 54.74; N, 12.94

EXAMPLE 21

4-Dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Hydrochloride



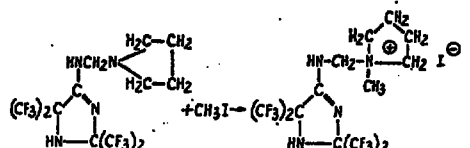
A solution of 2.5 g. of 4-dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline in 50 ml. of ether was saturated with dry hydrogen chloride gas. The white precipitate that formed was collected on a filter and washed with

ether. There was obtained 2.4 g. of the hydrochloride as colorless crystals, m.p. 160—165°C.

Anal. Calcd. for $C_{16}H_{11}F_{12}N_4Cl$: Cl, 7.87
Found: Cl, 7.24

EXAMPLE 22

4-(N-Methylpyrrolidiniummethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Iodide



Methyl iodide, 25 ml., was added to a solution of 5.0 g. of 4-(pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline in 25 ml. of ether. The solution was allowed to stand for three hours at 25°C. and the solid that precipitated during this time was collected on a filter and washed with ether. The solid (5.85 g.) was dissolved in acetone and fractionally precipitated by the addition of ether. The first fraction contained no fluorine and was discarded. 4-(N-Methylpyrrolidiniummethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline, 3.0 g., m.p. 190—193°C., was obtained as the last fractions. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a broad signal at τ 1.15 (NH), a singlet at τ 3.34 (NH), a doublet ($J=5.5$) at τ 4.60 (NCH_2N), a multiplet at τ 6.0 (4H), a singlet at τ 6.61 (CH_3), and a multiplet at τ 7.62 (4H). The F^{19} n.m.r. spectrum showed a pair of septets ($J=4.7$) at 70.9 and 76.8 p.p.m. from $CFCl_3$.

Anal. Calcd. for $C_{17}H_{12}F_{12}N_4I$:

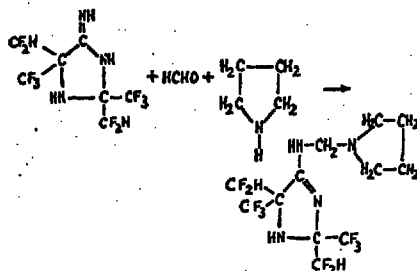
C, 26.82; H, 2.60; F, 39.16; I, 21.80; N, 9.62

Found: C, 27.01; H, 2.87; F, 38.73; I, 22.13; N, 9.25

EXAMPLE 23

4-(N-Pyrrolidylmethylamino)-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline

$R=H$; $X=N$ -pyrrolidylmethyl, $Z=Z^3=H$; $Z^1=Z^2=F$



A 2.0 g. sample of 4-imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazolidine was dissolved in 5 ml. of hot 37% formaldehyde (aqueous). The solution was cooled and mixed with 2 ml. of pyrrolidine. Water, 100 ml., was added, and the solid that separated was collected on a filter and washed with water. Recrystallization from pentane gave 1.15 g. of 4-(N-pyrrolidylmethylamino)-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline as colorless crystals, m.p. 97—99°C. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a triplet ($J=5.4$) at τ 3.54 (2H), a broad signal at τ 3.06 (NH), a singlet at τ 3.95, a doublet ($J=4.5$) at τ 5.54 and multiplets at τ 7.34 (4H) and τ 8.31 (4H). The F^{19} n.m.r. spectrum showed multiplets at 73.9 (3F), 77.8 (3F), 126.2 (2F) and 131.6 p.p.m. (2F).

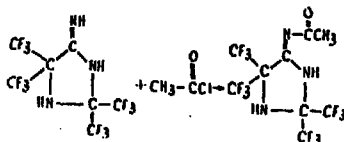
Anal. Calcd. for $C_{19}H_{14}F_{10}N_4$:

C, 35.65; H, 3.49; F, 47.00; N, 13.86

Found: C, 35.76; H, 3.53; F, 46.90; N, 13.53

EXAMPLE 24

4-Acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine
 $R=H$; $X=-COCH_3$; All $Z's=F$



A solution of 5.0 g. (0.014 mole) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 25 ml. of acetyl chloride was heated at reflux for 20 hours. The reaction mixture was then cooled and poured into 300 ml. of cold water to decompose the excess acetyl chloride. The solid that formed was collected on a filter and dried in air. There was obtained 5.32 g. (95% yield) of crude 4-acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as a white powder. Recrystallization from alcohol-water gave colorless needles, m.p. 154—155°C. (sealed cap.). The infrared spectrum contained bands at 5.79, 6.00 and 6.61 μ . The F^{19} n.m.r. spectrum in acetone showed two septets ($J=4.6$ c.p.s.) centered at 71.7 and 76.5 p.p.m. from CCl_3F used as an internal standard. The H^1 n.m.r. spectrum in $(CD_3)_2CO$ showed a sharp singlet at 2.37 p.p.m. (area 3) and two broad absorptions at 6.54 and 9.20 p.p.m. (area, 1 each) from $(CH_3)_4Si$ used as an internal reference. The ultraviolet absorption has a band at λ_{max}^{EtOH} 223m μ ($\epsilon=13,500$) with a shoulder at about 265 m μ that indicates the presence of a tautomeric form in ethanolic solution.

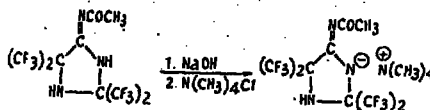
Anal. Calcd. for $C_9H_5F_{12}N_3O$:

C, 27.08; H, 1.26; F, 57.12; N, 10.53

Found: C, 27.52; H, 1.41; F, 58.14; N, 11.30

EXAMPLE 25

Tetramethylammonium Salt of 4-Acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine



A 10% sodium hydroxide aqueous solution was added dropwise to a suspension of 5.0 g. of 4-acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 25 ml. of water until solution was complete. The solution was filtered, and the filtrate was mixed with a solution of 5.0 g. of tetramethylammonium chloride in 10 ml. of water. The crystalline precipitate that formed upon cooling to 0°C. was collected on a filter and then recrystallized from alcohol-ether. There was obtained 4.1 g. of the tetramethylammonium salt as colorless crystals, m.p. 225—227°C. The infrared spectrum showed a strong absorption at 6.44 μ .

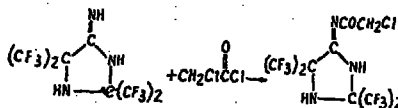
Anal. Calcd. for $C_{11}H_{11}F_{12}N_4O$:

C, 33.06; H, 3.42; F, 48.28; N, 11.86

Found: C, 33.43; H, 3.69; F, 47.74; N, 11.55

EXAMPLE 26

4-Chloroacetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine
 $R=H$; $X=-COCH_2Cl$; All $Z's=F$



A 5.0 g. sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 25 ml. (excess) of chloroacetyl chloride were refluxed for 3 days, the resulting reaction mixture poured onto ice-water (pentane used to facilitate transfer), and a solid (4 g.) was collected by suction filtration. The solid was recrystallized from ether-pentane giving 1.87 g., m.p. 143—144°C., of 4-chloroacetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine. Evaporation of the mother liquors gave 1.98 g. of additional

product. The mass spectrum showed a parent peak at m/e 433 and the expected fragmentation. H^1 n.m.r. showed bands at 4.62 p.p.m. ($-\text{CH}_2-$), 6.6 p.p.m. ($-\text{NH}-$ in the ring) and 9.6 p.p.m. ($-\text{NHCO}$) from $(\text{CH}_3)_4\text{Si}$ used as an internal standard. The F^{19} n.m.r. gave a characteristic pair of septets ($J=5$ c.p.s.) at +72.2 and 77.5 p.p.m. from ext. FCCl_3 at 56.4 Mc.

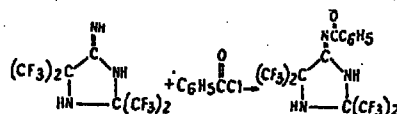
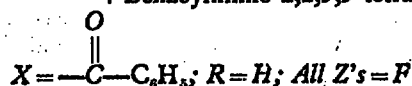
Anal. Calcd. for $\text{C}_9\text{H}_4\text{N}_2\text{OF}_{12}\text{Cl}$ (432.60):

C, 24.88; H, 0.93; N, 9.73; F, 52.6; Cl, 8.20

Found: C, 25.03; H, 1.07; N, 9.48; F, 53.04; Cl, 8.75

EXAMPLE 27

4-Benzoylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine



A 1.00-g. sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 0.410 g. of benzoyl chloride (1 equivalent) and 15 ml. of diethylene glycol dimethyl ether (diglyme) were refluxed for 3 days (most of the hydrogen chloride was given off within a few minutes). The reaction mixture was poured onto ice, diluted with water and extracted with ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the ether gave 0.85 g. of a solid which was recrystallized from ethanol-water giving 0.60 g. of white crystals, m.p. 157.5—159°C., which was 4-benzoylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine. The mass spectrum showed a parent peak at m/e 461 and the base peak at m/e 105 for $(\text{COC}_6\text{H}_5)^+$. The H^1 n.m.r. was consistent with the proposed structure and the F^{19} n.m.r. showed two multiplets at 72.5 and 77.6 p.p.m. from external FCCl_3 at 56.4 Mc. The UV showed λ_{max} 245 ($\epsilon=12,700$), 263 (11,100) m μ .

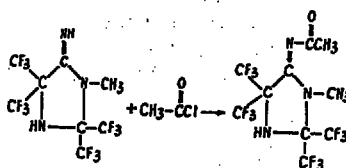
Anal. Calcd. for $\text{C}_{11}\text{H}_4\text{N}_2\text{OF}_{12}$ (461.22):

C, 36.45; H, 1.53; N, 9.12; F, 49.50

Found: C, 36.67; H, 1.59; N, 9.49; F, 49.85

EXAMPLE 28

4-Acetylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine



A mixture of 2.0 g. (0.0054 mole) of 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 5 ml. of acetyl chloride was heated at reflux for 30 hours and then cooled and poured over ice. The solid that formed was collected on a filter, washed with water, and recrystallized from alcohol-water. There was obtained 1.85 g. (83%) of 4-acetylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as colorless crystals, m.p. 137—139°C. The F^{19} n.m.r. spectrum in CD_3CN showed a septet ($J=4.2$ c.p.s.) at 73.1 p.p.m. and a multiplet at 75.1 p.p.m. from CCl_3F used as an internal standard. The H^1 n.m.r. spectrum in CD_3CN showed a singlet (area 3) at 2.17 p.p.m., a singlet (area 1, NH) at 2.33 p.p.m., and a septet ($J_{\text{HF}}=1$ c.p.s.) (area 3) centered at 3.02 p.p.m. lower field from $(\text{CH}_3)_4\text{Si}$ used as an internal reference. The ultraviolet spectrum showed λ_{max} 217 m μ ($\epsilon=8300$). The infrared spectrum showed bands at 5.75 μ and 6.00 μ .

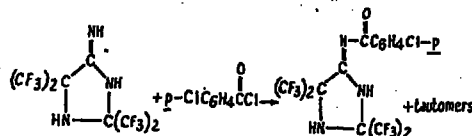
Anal. Calcd. for $\text{C}_{10}\text{H}_5\text{F}_{12}\text{N}_3\text{O}$:

C, 29.07; H, 1.71; F, 55.18; N, 10.17

Found: C, 29.37; H, 2.01; F, 54.92; N, 10.22

EXAMPLE 29

Preparation of 4-(*p*-Chlorobenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine
 $R=H$; $X=-COC_6H_4-Cl-p$; All $Z's=F$



A solution containing 5.0 g. (14.0 mmoles) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 2.5 g. (14.3 mmoles) of *p*-chlorobenzoyl chloride in 50 ml. of diglyme (diethylene glycol dimethyl ether) was refluxed, under a nitrogen atmosphere, until hydrogen chloride was no longer detected when the condenser outlet adapter was bubbled into silver nitrate solution, 15 hours being required. The cooled reaction solution was poured into 150 ml. of water and the resulting solid was filtered, dissolved in methanol and precipitated with water. The filtered product was dissolved in 75 ml. of diethyl ether and extracted with 5 ml. of 5% sodium bicarbonate. The ether layer was washed with water, dried over anhydrous magnesium sulfate, then filtered. Crystallization from ether-petroleum ether (3:1) mixture, filtering and drying in a vacuum oven at 60°C. for 12 hours gave 3.3 g. of 4-(*p*-chlorobenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white crystals, m.p. 139–140°C.

Anal. Calcd. for $C_{14}H_6ClF_{12}N_3O$:

C, 33.93; H, 1.22; Cl, 7.15; F, 46.06; N, 8.48; M.W., 495.57

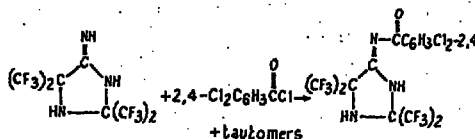
Found: C, 34.29; H, 1.52; Cl, 7.85; F, 45.33; N, 8.44

The mass spectrum contained the parent peak at 495 m/e. The F^{19} n.m.r. spectrum, obtained in deuteroacetone with $(CH_3)_4Si$ as internal reference and $FeCl_3$ as external reference, contained four broad bands in equal intensity with centers at 73.3, 74.5, 79.1 and 79.5 p.p.m. The proton n.m.r. spectrum contained a broad band at 6.8 p.p.m. [$H-N-(1)$]. The A_2B_2 pattern for aromatics was centered at 7.78 p.p.m. with A_2 part centered at 7.55 p.p.m. ($J=8.5$ c.p.s.) (2H). The B_2 part was centered at 8.05 p.p.m. ($J=8.5$ c.p.s.) and was distorted by the (NH) which gave a broad band from 7.8 to 10.15 p.p.m. (3H). When trifluoroacetic acid was added the high field (NH) was shifted and appeared as a sharp singlet at 6.72 p.p.m.; the low field (NH) was removed and the aromatics gave a typical A_2B_2 pattern centered at 7.78 p.p.m. ($J=8.5$ c.p.s.) (4H). The ultraviolet spectrum in acetonitrile showed $\lambda_{max}=250$ m ($\epsilon=19,330$), and in ethanol the spectrum contained two bands at λ_{max} 253, 270 m μ .

EXAMPLE 30

Preparation of 4-(2,4-Dichlorobenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R=H$; $X=-COC_6H_3Cl_2-2,4$; All $Z's=F$



The procedure of Example 29 was repeated with the exceptions that 3.0 g. (14.3 mmoles) of 2,4-dichlorobenzoyl chloride was substituted for the *p*-chlorobenzoyl chloride of that example and the refluxing of the reaction mixture was continued for 40 hours. There was obtained 4.5 g. of 4-(2,4-dichlorobenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white needles, m.p. 153.4–153.8°C.

Anal. Calcd. for $C_{14}H_5Cl_2F_{12}N_3O$:

C, 31.72; H, 0.95; Cl, 13.38; F, 43.02; N, 7.93; M.W., 530.02

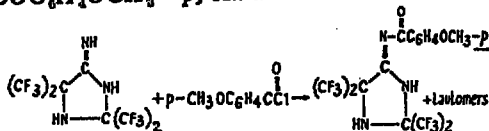
Found: C, 32.40; H, 1.16; Cl, 14.00; F, 42.23; N, 7.79

The mass spectrum contained the parent peak at 529 m/e, based on the most abundant Cl^{35} ion. The F^{19} n.m.r. spectrum, obtained in deuteroacetone with $(CH_3)_4Si$ as internal reference and with $FeCl_3$ as external reference, contained two broad bands in equal intensity with centres at 73.2 and 78.7 p.p.m. The proton n.m.r. spectrum contained a singlet at 6.56 p.p.m. [$H-N-(1)$], a multiplet typical of an ABC pattern for aromatics centered at 7.5 p.p.m. (3H), and a broad band at 10.1 p.p.m. (NH), which exchanged with trifluoroacetic acid. The ultraviolet absorption in acetonitrile showed $\lambda_{max}=216$ m μ ($\epsilon=23,400$).

EXAMPLE 31

Preparation of 4-(*p*-Methoxybenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine

$R=H$; $X=-COC_6H_4OCH_3-p$; All $Z's=F$



The procedure of Example 29 was repeated with the exceptions that 2.5 g. (14.3 mmoles) of *p*-methoxybenzoyl chloride was substituted for the *p*-chlorobenzoyl chloride of that example and the refluxing of the reaction mixture was carried out for 24 hours. There was obtained 2.5 g. of 4-(*p*-methoxybenzoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white crystals, m.p. 122.8—124.2°C.

Anal. Calcd. for $C_{15}H_5F_{12}N_3O_2$:

C, 36.76; H, 1.85; F, 46.54; N, 8.56; M.W., 491.16

Found: C, 37.05; H, 1.89; F, 45.20; N, 8.80

The mass spectrum contained the parent peak at 491 m/e. The F^{19} n.m.r. spectrum, obtained as described in Example 30, contained four broad bands: two in equal intensity centered at 72.1 and 77.3 p.p.m. and two in equal intensity centered at 73.8 and 78.4 p.p.m. The ratio of the low field set to the high field set was about 5:4, respectively.

The proton n.m.r. spectrum contained a sharp singlet at 3.9 p.p.m. (CH_3O), and a broad band centered at 6.7 p.p.m. [$H-N-(1)$]. The A_2B_2 pattern for aromatics was distorted by the low field (NH) which appeared at 7.25 to 9.3 p.p.m. (3H) and included the B_2 part appearing as a broad band centered at 8.0 p.p.m. The A_2 part was centered at 7.04 p.p.m. ($J=9$ c.p.s.) (2H). When trifluoroacetic acid was added, the high field (NH) was shifted and appeared as a sharp singlet at 5.65 p.p.m.; the low field (NH) was removed and the aromatics gave a typical A_2B_2 pattern centered at 7.5 p.p.m. ($J=9$ c.p.s.) (4H). The ultraviolet absorption in acetonitrile showed $\lambda_{max}=220$ m μ ($\epsilon=16,800$); $\lambda_{max}=278$ m μ ($\epsilon=17,100$).

EXAMPLE 32

4-(Crotonylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R=H$; $X=-COCH=CHCH_3$; All $Z's=F$ (with isomers and tautomers)

The procedure of Example 29 was repeated with the exceptions that 7.0 g. (19.6 mmole) of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was used, 2.0 g. (20.0 mmoles) of crotonyl chloride was substituted for *p*-chlorobenzoyl, and the refluxing of the reaction mixture was continued for 63 hr. Fractional recrystallization of 4.8 g. of solid product from chloroform gave *cis* and *trans* isomers and a 0.7 g. *cis-trans* mixture of 4-(crotonylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white crystals, m.p. 208.8—213.8°C.

Anal. Calcd. for $C_{11}H_7F_{12}N_3O$:

C, 31.08; H, 1.66; F, 53.64; N, 9.89

Found: C, 30.86; H, 1.73; F, 53.13; N, 9.68 for *cis/trans* mixture

The infrared, proton and fluorine n.m.r. spectra were consistent.

EXAMPLE 33

4-(Heptanoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (and tautomers)

$R=H$; $X=-CO(CH_2)_5CH_3$; All $Z's=F$

The procedure of Example 32 was repeated with the exception that 3 g. (20 mmole) of *n*-heptanoyl chloride was substituted for the crotonyl chloride of that example. Recrystallization of 5.5 g. of solid product from chloroform gave 1.6 g. of 4-(heptanoylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white needles, m.p. 87.5—88.0°C.

Anal. Calcd. for $C_{14}H_{11}F_{12}N_3O$:

C, 35.85; H, 3.22; F, 48.82; N, 8.96

Found: C, 35.49; H, 3.13; F, 48.06; N, 8.69

The infrared, proton and fluorine n.m.r. spectra were consistent.

EXAMPLE 34

4-(Dichloroacetylmino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (and tautomers)
 $R=H$; $X=-COCHCl_2$; All $Z's=F$

The procedure of Example 32 was repeated with the exception that 25 ml. of dichloroacetyl chloride was substituted for the crotonyl chloride of that example. Recrystallization of 6 g. of solid product from ether/pentane gave 1 g. of 4-(dichloroacetylmino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white crystals, m.p. 100.2—101.2°C. (sealed cap.)

Anal. Calcd. for $C_9H_3F_{12}Cl_2N_2O$:

C, 23.10; H, 0.64; Cl, 15.15; F, 48.72; N, 8.98; M.W., 468.06

Found: C, 22.95; H, 0.63; Cl, 14.91; F, 47.71; N, 8.95

The mass spectrum contained the parent peak at 467 m/e, based on the most abundant Cl^{35} ion.

The infrared, ultraviolet and n.m.r. spectra were consistent and indicated tautomers.

EXAMPLE 35

4-(2,4-Dichlorophenoxyacetylmino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine (and tautomers)

$R=H$; $X=-COCH_2OC_6H_3Cl_2-2,4$; All $Z's=F$

The procedure of Example 29 was repeated with the exceptions that 3.5 g. (14.6 mmole) of 2,4-dichlorophenoxyacetyl chloride was substituted for the *p*-chlorobenzoyl chloride of that example and the refluxing of the reaction mixture was continued for 24 hours. There was obtained 2.0 g. of 4-(2,4-dichlorophenoxyacetyl)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine as white crystals, m.p. 197—197.9°C.

Anal. Calcd. for $C_{15}H_7Cl_2F_{12}N_2O_2$:

C, 32.17; H, 1.26; F, 40.72; N, 7.50; M.W., 560.051

Found: C, 32.36; H, 1.32; F, 39.69; N, 7.02

The mass spectrum contained the parent peak at 559 m/e based on most abundant Cl^{35} ion. The infrared and n.m.r. spectra were consistent; the ultraviolet spectra indicated tautomerization.

When the procedures similar to those described in Examples 24 and 26—35 are carried out with appropriate acid chlorides and imidazolidines substituted for the specific acid chlorides and imidazolidine of those examples, the following acyl derivatives of 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidines can be prepared:

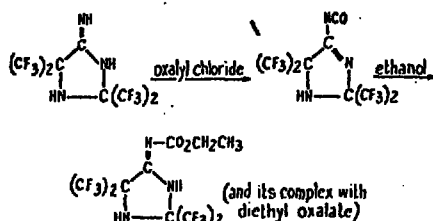
- 4-Propionylimino-2,2,5,5-tetrakis(difluoromethyl)imidazolidine;
- 4-Octanoylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-Undecanoylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-Trifluoroacetylmino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(3-Chlorobutyryl)imino-2,2,5,5-tetrakis(difluoromethyl)imidazolidine;
- 4-(2-Bromopropionyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-Methoxyacetylmino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)imidazolidine;
- 4-Butoxyacetylmino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)imidazolidine;
- 4-(β -Ethoxypropionyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-Naphthoylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(*p*-Fluorobenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(2,4,6-Trichlorobenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(*p*-Bromobenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(2,4-Diethylbenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-Cumoylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
- 4-(*p*-Methoxybenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine; and
- 4-(*p*-Butoxybenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

When amino- or alkyl-substituted aminoacyl derivatives are desired, they can be prepared by first reacting the 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidine with a nitroacyl chloride to form the corresponding 4-nitroacylimino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidine. This nitroacyl derivative can then be reduced by treatment with hydrogen in the presence of a hydrogenation catalyst such as platinum to form the aminoacylimino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidine. The alkyl- and dialkylaminoacylimidazolidine can be prepared by alkylating the 4-aminoacylimino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidine with alkylating agents having alkyl moieties of 1—4 carbon atoms such as dimethyl sulfate. The following aminoacyl derivatives of 4-imino-2,2,5,5-tetrakis(polyfluoromethyl)imidazolidine can be prepared in this manner:

4-(Aminoacetylino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
 4-(α -Aminopropionyl)imino-2,2,5,5-tetrakis(difluoromethyl)imidazolidine;
 4-Butylaminoacetylino-2,2,5,5-tetrakis(difluoromethyl)imidazolidine;
 4-[α -(Dipropylamino)propionyl]imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine;
 4-(*p*-Aminobenzoyl)imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-imidazolidine;
 4-(*p*-Butylaminobenzoyl)imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine; and
 4-(*p*-Diethylaminobenzoyl)imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)imidazolidine.

EXAMPLE 36

4-(Carbethoxyimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine
 $R=H$; $X=COO-CH_2CH_3$; All $Z's=F$



A 5.0 g. sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine dissolved in 20 ml. of glyme (ethylene glycol dimethyl ether) was added over 0.5 hour to 4.0 ml. of oxalyl chloride (excess) in 20 ml. of glyme (yellow color). After the addition was complete the infrared spectrum of the reaction mixture showed no bands in the isocyanate region. After stirring at room temperature for 20 minutes, a weak band at 4.41μ appeared in the infrared indicating the formation of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline. After refluxing for 30 minutes, the yellow color had completely disappeared and the infrared spectrum now showed a strong isocyanate band at 4.41μ . After another 15 minutes of reflux, 10 ml. of absolute ethanol was added (infrared analysis showed the absence of the isocyanate band indicating that the isocyanate had reacted with ethanol). Evaporation of the glyme and excess ethanol under reduced pressure gave a white semisolid which on washing with pentane gave 4.82 g. of a white solid, m.p. $70-120^\circ\text{C}$.

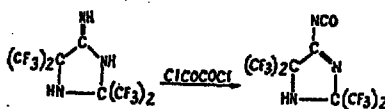
The pentane-washed solid was recrystallized from ether-pentane to give 0.86 g. of white solid, m.p. $122-124^\circ\text{C}$., which was the carbethoxyimine. H^1 n.m.r. showed a CH_3 triplet ($J=7.0$) at 1.27 p.p.m. and a CH_2 quartet ($J=7.0$) at 4.23 p.p.m. and NH bands at 6.48 p.p.m. and 9.22 p.p.m. lower field from $(\text{CH}_3)_4\text{Si}$ used as an internal reference.

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{O}_2\text{F}_{12}$ (429.18):

C, 27.99; H, 1.64; N, 9.80; F, 53.1

Found: C, 28.25; H, 1.95; N, 9.87; F, 53.24

The 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline formed as an intermediate in the process of Example 36 can be isolated, if desired, by carrying out the first step of the process of that example as follows:



Essentially anhydrous conditions were maintained. A three-necked flask attached to the bottom of a spinning band fractionating column was equipped with a magnetic stirrer, nitrogen inlet and dropping funnel. The equipment was flame-dried, cooled and 15 ml. of oxalyl chloride and 75 ml. of anhydrous diethyl ether were introduced into the flask under positive nitrogen pressure. Then a solution of 30 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine dissolved in 100 ml. of ether was added over 30 minutes with vigorous stirring. After stirring an additional 20 minutes, the ether was removed by distillation at a moderate rate and the residue distilled at 75 mm. The product, 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline, b.p. 78°C . (75 mm.), 25.7 g., was collected in oven-dried vials (as it reacts with moist air). H^1 n.m.r. showed a singlet (broad) at 3.6 p.p.m. F^{19} n.m.r. showed a pair of septets ($J=5$) at +73.3 and +78.0 p.p.m. from external FeCl_3 at 56.4 M.

Anal. Calcd. for $C_8H_8N_2O_2F_{12}$ (383.12):

C, 25.08; H, 0.26; N, 10.96

Found: C, 25.58; H, 0.77; N, 11.51

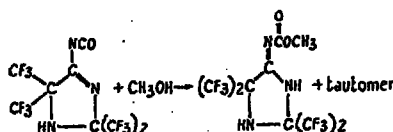
When the process of Example 36 is repeated with other alcohols substituted for the ethanol used to react with the isocyanate intermediate formed in that example, the following carbalkoxyiminoimidazolidines can be obtained:

4-Carbocyclohexoxyimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine; and
4-Carbobutoxyimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

EXAMPLE 37

4-(Carbomethoxyimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R=H$; $X=-COOCH_3$; All $Z's=F$



A 25 ml. sample (excess) of methanol was mixed at room temperature with a 6.2-g. portion of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline dissolved in 100 ml. of ether. Evaporation of the reaction mixture to dryness gave 6.98 g. of a white solid, m.p. 116–120°C. Recrystallization of one-half of this material from methanol-water gave 2.56 g. (76%) of the urethane product, m.p. 125–129°C. This material did not absorb in the ultraviolet above 210 m μ . The H^1 n.m.r. showed $-OCH_3$ absorption at τ 6.20 and NH bands at τ 3.5 and τ 0.2. F^{19} n.m.r. showed a pair of septets ($J=5$) at 72.1 and 75.6 p.p.m. from ext. CCl_4 .

Anal. Calcd. for $C_{10}H_8N_2O_2F_{12}$ (415.15)

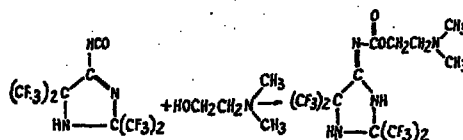
C, 26.04; H, 1.21; N, 10.13; F, 54.92

Found: C, 26.30; H, 1.39; N, 10.44; F, 53.65

EXAMPLE 38

4-(2-Dimethylaminoethoxycarbonylimino)-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine

$R=H$; $X=-COOCH_2CH_2N(CH_3)_2$; All $Z's=F$



A 6.2 g. sample of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline was added at room temperature to 1.44 g. (1 equiv.) of dimethylaminoethanol dissolved in 100 ml. of ether. An exothermic reaction took place and in a few minutes a white precipitate formed. The solid was collected and washed with ether, 4.74 g. (62%), m.p. 136–141°C. The H^1 n.m.r. showed NH bands at τ 1.0 and 4.48, $-OCH_2-$ at τ 5.6 and $-CH_2N$ at τ 6.6 forming an A_2B_2 pattern ($J=6$) and $-N(CH_3)_2$ at τ 7.1. The F^{19} n.m.r. showed a pair of septets ($J=5$) at 71.7 and 76.9 p.p.m. for int. CCl_4 . The ultraviolet spectrum showed λ_{max} 252 m μ ($k=27.2$ in CH_3CN and 11.7 in ethanol), indicating a tautomeric mixture. The hydrochloride was prepared and found to be water soluble.

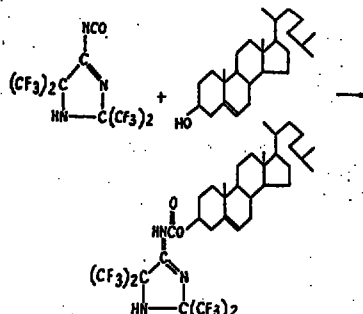
Anal. Calcd. for $C_{12}H_{12}N_4O_2F_{12}$ (472.25):

C, 30.52; H, 2.56; N, 11.87; F, 48.4

Found: C, 30.92; H, 2.82; N, 12.14; F, 48.94

EXAMPLE 39

4-Isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Cholesterol Ester
 $R=H$; $X=-COOC_{27}H_{53}$; All $Z's=F$



A 7 g. sample of freshly prepared 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline was distilled into a solution of 7.7 g. of dry cholesterol dissolved in ca. 70 ml. of glyme (ethylene glycol dimethyl ether). The residue was removed by evaporation under reduced pressure and the residue was sublimed giving 11.3 g. (77%) of adduct, m.p. 169–172°C. The F^{19} n.m.r. showed a pair of multiplets at 71.8 and 77.1 p.p.m. from ext. $FCCl_3$.

Anal. Calcd. for $C_{35}H_{47}N_3F_{12}O_2$ (769.76):

C, 54.61; H, 6.14; N, 6.26; F, 29.6

Found: C, 55.58; H, 6.25; N, 5.54; F, 28.13

Many of the imidazolidines and 3-imidazolines of the invention are stable in contact with metal surfaces such as iron, steel, stainless steel, nickel and copper, even at elevated temperatures, and can therefore be employed in applications which involve prolonged contact with these metals. Such applications include heat exchange fluids and high temperature hydraulic fluids. The stability of these imidazolidines is illustrated by the following experiments:

EXAMPLE A

A 0.5 g. sample of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazoline was sealed with an iron wire and a copper wire in a glass tube and was heated at 437°F. for 44 hours. No change in either the fluid or the metal wires was observed during this period.

EXAMPLE B

A 0.5 g. sample of 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was sealed with an iron wire and a copper wire in a glass tube and heated at 437°F. for 20 hours. No change in either the fluid or the metal wires was observed during this period.

EXAMPLE C

A 0.5 g. sample of 4-acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine was sealed with a copper wire in a glass tube and heated at 437°F. for 20 hours. No change in either the fluid or the copper wire was observed during this time.

All the compounds of this invention are useful for modifying polymers. Such modifications include lowering the forming temperatures or pressures, or plasticizing the polymers:

The modification of poly(methyl methacrylate) resin is illustrated by the following experiment:

EXAMPLE D

The following compositions were prepared:

(a) A mixture of 0.5 g. of poly(methyl methacrylate) resin and 0.1 g. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

(b) A mixture of 0.5 g. of poly(methyl methacrylate) resin and 0.1 g. of 4-acetylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

(c) A mixture of 0.5 g. of poly(methyl methacrylate) resin and 0.1 g. of 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

(d) A mixture of 0.5 g. of poly(methyl methacrylate) resin and 0.1 g. of 4-benzylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline.

(e) A mixture of 0.5 g. of poly(methyl methacrylate) resin without additives. Circular films were pressed from a compact pile of each composition at 150°C. and 5000 lbs. ram pressure for 10 seconds.

The film pressed from composition (a) was 9 mils thick and 2 inches in diameter.

The film pressed from composition (b) was 11 mils thick and $1\frac{1}{8}$ inches in diameter.

The film pressed from composition (c) was 11.5 mils thick and $1\frac{1}{4}$ inches in diameter.

The film pressed from composition (d) was 8.5 mils thick and $2\frac{1}{8}$ inches in diameter.

The film pressed from composition (e) was 18.5 mils thick, only $1\frac{1}{8}$ inches in diameter, and was incompletely coalesced around the edges.

This experiment shows that the forming temperatures or pressures for poly-(methyl methacrylate) resin are lowered by the addition of the imidazolidines of this invention.

An excellent method for demonstrating muscle-relaxant activity is the use of the 30° Inclined Screen Test of L. O. Randall et al. [*J. Pharm. Exp. Therap.*, 129, 163 (1960)]. This test determines the oral dose which causes 50% of the test animals (mice) to lose their footing on a wire mesh which is inclined 30° from the horizontal. This is called the "paralyzing dose₅₀" or PD₅₀ value. In this test, low PD₅₀ values indicate high potencies.

Another excellent method for demonstrating muscle relaxant activity is the Wire Lift Test. The forefeet of albino mice are placed on a taut wire stretched at a level of approximately 12 inches over a flat surface. Normal animals grasp the wire and lift their hind feet to the wire, where balance is maintained. Inability to lift the hind legs to the wire is taken as a positive response and is considered to be a measure of muscle relaxation. This test determines the oral dose which imparts to 50% of the test animals (mice) an inability to lift their hind legs to the wire, and which is called the "effective dose₅₀" or ED₅₀ value. Dose response relationships are determined by the method of L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.* 57, 261-264 (1944).

The following table gives PD₅₀ and ED₅₀ values for representative compounds of this invention.

TABLE
Results of Tests for Muscle Relaxant Activity

Product of Example No.	Compound	Inclined Screen PD ₅₀ (mg./kg.)	Wire Lift ED ₅₀ (mg./kg.)
1-B, 2	4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	10.6 ± 0.9	7.0 ± 0.51
3	4-Imino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)imidazolidine	17.3 ± 1.3	10.0 ± 0.83
4	4-Imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)-imidazolidine	20.5 ± 1.7	13.0 ± 1.3
4	3-Methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	30.0 ± 3.3	19.5 ± 2.3
5	3-Ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	17.0 ± 1.4	12.3 ± 1.0
7	3-Ethyl-4-ethylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	57.0 ± 14.0	30.0 ± 3.9
7	4-Ethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazolidine	17.5 ± 2.4	8.3 ± 0.75
8	3-Ethyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	—	30.0 ± 3.3
9	4-Ethylimino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	—	22.0 ± 1/.6
10	4-Benzylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline	45.0 ± 7.6	30.0 ± 5.4

TABLE (Continued)

Product of Example No.	Compound	Inclined Screen PD ₅₀ (mg./kg.)	Wire Lift ED ₅₀ (mg./kg.)	
11	4-Allylamino-2,2,5,5-tetrakis (trifluoromethyl)-3-imidazoline	41.0 ± 4.8	28.0 ± 3.0	5
12	4-Methylamino-2,2,5,5-tetrakis (trifluoromethyl)-3-imidazoline	18.8 ± 1.3	10.8 ± 0.86	10
14	4-Hydroxymethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline	13.2 ± 1.6	5.6 ± 0.85	15
15	4-(Hydroxymethoxymethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline	16.0 ± 1.3	7.6 ± 1.0	20
17	4-(N-Pyrrolidylmethylamino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Hydrochloride	18.8 ± 1.7	10.5 ± 0.7	25
20	4-Dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline	22.0 ± 1.8	10.0 ± 1.1	30
21	4-Dimethylaminomethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline Hydrochloride	19.2 ± 1.2	7.5 ± 1.2	35
24	4-Acetylmino-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	24.0 ± 1.9	13.4 ± 1.1	40
25	Tetramethylammonium Salt of 4-Acetylmino-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	16.0 ± 1.6	8.8 ± 1.03	45
26	4-Chloroacetylmino-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	16.5 ± 1.4	9.8 ± 0.77	50
28	4-Acetylmino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine	24.0 ± 2.5	15.0 ± 0.85	
33	4-(Heptanoylimino)-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	28.5 ± 2.9	10.0 ± 0.6	
36	4-(Carbomethoxyimino)-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	14.5 ± 1.4	10.2 ± 0.87	
37	4-(Carbomethoxyimino)-2,2,5,5-tetrakis (trifluoromethyl)imidazolidine	17.0 ± 1.0	11.5 ± 1.1	
38	4-(2-Dimethylaminoethoxy-carbonylimino)-2,2,5,5-tetrakis (trifluoromethyl)-imidazolidine Hydrochloride	33.5 ± 3.2	19.2 ± 1.9	

In pharmaceutical application, the compounds of this invention will be administered to the body orally, parenterally and by other methods. The dosage will vary and will depend on such factors as the condition being treated; age and weight of the recipient; the responsiveness of the recipient; prior, concurrent and intended subsequent medication and treatment; general health of the recipient, frequency of treatment; and of course the nature of the effect desired.

Generally speaking, the active compound will be administered in a physiologically beneficial amount. Administration can be in a single dose or in a plurality of doses over an extended period of time. It will of course also be understood that an initial dose, or first group of doses, in a course of treatment, can be in greater amounts if appropriate, and a rapid response is sought by the early administration of relatively large doses and there after the minimally effective dosage, or maintenance dosage, is determined.

A single dose will rarely exceed about 10 or 20 milligrams of active compound per kilogram within this invention, although larger amounts can be used as called for in any given situation. Extremely small doses will effect some benefit but as a practical matter a single dose of less than about 0.001 to 0.002 milligram per kilogram will seldom be used. Ordinarily, doses will range from 0.05 to 10 mg./kg. and preferably 0.05 to 5 mg./kg. Doses can be repeated in the same or greater or lesser amounts over a period of time as long as improvement in the recipient is observed or as long as needed under the circumstances.

The compound will ordinarily be administered with a non-toxic pharmaceutical carrier in a variety of practical dosage forms. These dosage forms are novel compositions comprising the non-toxic pharmaceutical carrier and a physiologically beneficial amount of the active compound. These highly useful dosage forms constitute an important aspect of the present invention.

Suitable non-toxic pharmaceutical carriers or vehicles include liquids such as water, aromatic water, alcohols, syrups, elixirs, pharmaceutical mucilages, such as acacia and tragacanth, oils of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil, or fish oil such as cod liver oil, for oral administration; water, saline, aqueous lactose, aqueous maltose, aqueous glucose (dextrose) or aqueous sucrose, for administration by injection. Suitable solid carriers include soft gelatin capsules, hard gelatin capsules, slow or delayed release pills or capsules, powders, or tableting vehicles. Suitable solid or liquid non-toxic pharmaceutical carriers are well known in the art and the selection of carrier can be from those appropriate and available in accordance with well-known prescription techniques. The compositions of this invention therefore include such dosage forms as solutions, suspensions, syrups, elixir, tablets, capsules, and powder packets.

A vast number of suitable pharmaceutical carriers are described in "Remington's Practice of Pharmacy," edited by E. W. Martin and E. F. Cook, 12th Ed., 1961, published by the Mack Publishing Company, Easton, Pennsylvania.

In these novel compositions the new active compounds of this invention will be present in a physiologically beneficial amount as mentioned above. In practice, this means that the active ingredient will ordinarily constitute at least about 0.001% by weight based on the total weight of the composition. For oral administration in liquid medium, the concentration will ordinarily be in the range from about 0.01—2.0% by weight of active ingredient. For injection, concentrations from 0.005—0.5% are satisfactory. In tablets, powders and capsules, the amount of active ingredient may if desired be as much as 10 to 50% or more by weight of the total composition.

The active compounds of this invention can be formulated if desired with one or more pharmaceutically active materials for combination effects, treatments and benefits. Such materials include but are by no means limited to antidepressants or stimulants, vitamins, pain killers, tranquilizers, antibiotics and antitussive agents. The compositions can of course contain suitable pharmaceutical modifiers such as coloring agents, sweetening or other flavoring agents or solubilizing agents, as will readily occur to persons skilled in this art.

The following further examples illustrate specific pharmaceutical compositions for administration to a living body:

EXAMPLE E

4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine is formulated conveniently in ethyl alcohol USP-water in 0.05% by weight concentration for oral administration, with or without a flavoring agent, and a coloring agent; and in 0.5, 1, 5, 10, and 25 milligram amounts in standard two-piece hard gelatin capsules with a diluent such as starch, mannitol or lactose, for oral administration. In pharmacological applications

it is administered in these dosage forms at dosage levels in the range of 0.5 to 100 milligrams for treatment of physiological conditions as described above.

Similar formulations are made with 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

EXAMPLE F

4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine can be formulated with suitable tableting adjuvants using a conventional tableting machine with the active ingredient constituting 1—50% by weight of the tablet. Other ingredients include gelatin, magnesium stearate, and starch or mannitol.

Formulations of the type illustrated by Example F are also made with any of the active solid compounds of this invention.

EXAMPLE G

4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine can be formulated in a soft gelatin capsule by dissolving the compound in polyethylene glycol (of molecular weight of about 400) or soybean oil in concentrations of 0.05 to 10% weight/volume. The solution containing the compound is injected into the gelatin to form the capsule using a positive displacement pump set to deliver a specific volume depending on the dose required. The capsules are then dried before use.

Capsules prepared thus can be administered from 1 to 6 times daily to patients for relief of various types of muscle disorder.

Soft gelatin capsule formulations of the type of Example G are also made with compounds such as 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazoline, 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 4-imino-2,5-bis(difluoromethyl)-2,5-bis-(trifluoromethyl)imidazolidine, and 4-hydroxymethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline.

EXAMPLE H

No. 5 two-piece hard gelatin capsules can be filled with 110 mg. of a mixture consisting of 1.0 mg. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 0.2 mg. of the finely divided, fumed silicon dioxide known commercially as Cab-O-Sil and approximately 109 mg. of lactose.

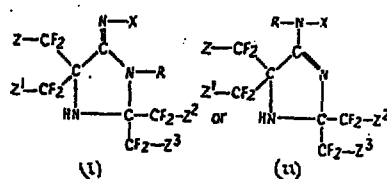
Any of the active compounds of this invention can be used in formulations of the type illustrated by Example H.

EXAMPLE I

A flavored syrup containing 1 mg. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 5 ml. can be prepared by dissolving the compound in a flavored solution of sorbitol containing up to 50% of ethyl alcohol USP so that the final concentration is 0.02% weight/volume.

WHAT WE CLAIM IS:—

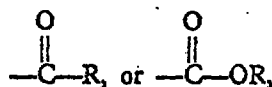
1. A compound of the general formula



wherein:

(A) R is (1) hydrogen, (2) hydrocarbyl or (3) hydrocarbyl substituted with at least one of the following: up to 6 halogens of atomic number 9—35, inclusive; —OH; —NH₂; hydrocarbyloxy; hydrocarbylamino; or hydrocarbyloxy or hydrocarbylamino containing O or N in the hydrocarbon chain and/or substituted by —OH, —NH₂, —COOH, —COOM (where M is an alkali metal or an equivalent of an alkaline earth metal) or halogen of atomic number 9—35;

(B) X is one of the atoms and groups defined above for R,



it is administered in these dosage forms at dosage levels in the range of 0.5 to 100 milligrams for treatment of physiological conditions as described above.

Similar formulations are made with 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine and 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine.

EXAMPLE F

4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine can be formulated with suitable tableting adjuvants using a conventional tableting machine with the active ingredient constituting 1—50% by weight of the tablet. Other ingredients include gelatin, magnesium stearate, and starch or mannitol.

Formulations of the type illustrated by Example F are also made with any of the active solid compounds of this invention.

EXAMPLE G

4-Imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine can be formulated in a soft gelatin capsule by dissolving the compound in polyethylene glycol (of molecular weight of about 400) or soybean oil in concentrations of 0.05 to 10% weight/volume. The solution containing the compound is injected into the gelatin to form the capsule using a positive displacement pump set to deliver a specific volume depending on the dose required. The capsules are then dried before use.

Capsules prepared thus can be administered from 1 to 6 times daily to patients for relief of various types of muscle disorder.

Soft gelatin capsule formulations of the type of Example G are also made with compounds such as 3-methyl-4-methylimino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 3-ethyl-4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 4-imino-3-methyl-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 4-imino-2,5-bis(difluoromethyl)-2,5-bis-(trifluoromethyl)imidazolidine, and 4-hydroxymethylamino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline.

EXAMPLE H

No. 5 two-piece hard gelatin capsules can be filled with 110 mg. of a mixture consisting of 1.0 mg. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine, 0.2 mg. of the finely divided, fumed silicon dioxide known commercially as Cab-O-Sil and approximately 109 mg. of lactose.

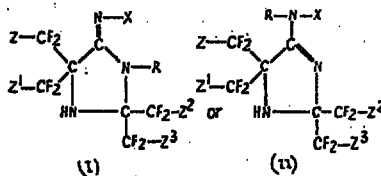
Any of the active compounds of this invention can be used in formulations of the type illustrated by Example H.

EXAMPLE I

A flavored syrup containing 1 mg. of 4-imino-2,2,5,5-tetrakis(trifluoromethyl)imidazolidine in 5 ml. can be prepared by dissolving the compound in a flavored solution of sorbitol containing up to 50% of ethyl alcohol USP so that the final concentration is 0.02% weight/volume.

WHAT WE CLAIM IS:—

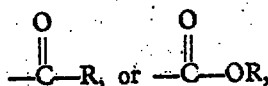
1. A compound of the general formula



wherein:

(A) R is (1) hydrogen, (2) hydrocarbyl or (3) hydrocarbyl substituted with at least one of the following: up to 6 halogens of atomic number 9—35, inclusive; —OH; —NH₂; hydrocarbyloxy; hydrocarbylamino; or hydrocarbyloxy or hydrocarbylamino containing O or N in the hydrocarbon chain and/or substituted by —OH, —NH₂, —COOH, —COOM (where M is an alkali metal or an equivalent of an alkaline earth metal) or halogen of atomic number 9—35;

(B) X is one of the atoms and groups defined above for R,



R being as above; and

(C) Z, Z', Z² and Z³, alike or different, are hydrogen or fluorine;

(D) With the proviso that R and X together contain no more than 30 carbon atoms.

2. 4 - [1 - amino - 2,2,2 - trifluoro - 1 - (trifluoromethyl) ethylamino] - 2,2,5,5-tetrakis (trifluoromethyl) - 3 - imidazoline. 5

3. 4 - [1 - amino - 2,2 - difluoro - 1 - (trifluoromethyl)ethylamino] - 2,5 - bis-(difluoromethyl) - 2,5 - bis (trifluoromethyl) - 3 - imidazoline.

4. 4 - imino - 2,2,5,5 - tetrakis(trifluoromethyl)imidazolidine, its tautomeric imidazoline form (as defined in Claim 1), or a mixture thereof. 10

5. 4 - imino - 2,5 - bis(difluoromethyl) - 2,5 - bis(trifluoromethyl)imidazoline, its tautomeric imidazoline form (as defined in Claim 1), or a mixture thereof.

6. 4 - hydroxymethylamino - 2,2,5,5 - tetrakis(trifluoromethyl) - 3 - imidazoline.

7. 4 - dimethylaminomethylamino - 2,2,5,5 - tetrakis(trifluoromethyl) - 3 - imidazoline. 15

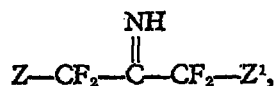
8. 3 - ethyl - 4 - imino - 2,2,5,5 - tetrakis(trifluoromethyl)imidazolidine.

9. 4 - (hydroxymethoxymethylamino) - 2,2,5,5 - tetrakis(trifluoromethyl) - 3 - imidazoline.

10. 4 - (N - methylpyrrolidiniummethylamino) - 2,2,5,5 - tetrakis - (trifluoromethyl) - 3 - imidazoline iodide. 20

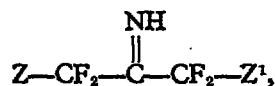
11. 4 - acetylmino - 2,2,5,5 - tetrakis - (trifluoromethyl)imidazolidine.

12. A process for preparing a compound according to Claim 1 wherein R is H and X is polyfluoromethylethylamino, in which an alkali metal cyanide is reacted with one polyfluoroalkylidenimine of the formula



Z and Z' being as in Claim 1, where a compound is required having Z² and Z³ respectively identical with Z and Z', or the cyanide is reacted with more than one such polyalkylidenimine where a compound is required having Z² and/or Z³ different from Z and Z', under conditions which avoid elimination of the polyfluoromethylethylamino substituent, and the compound containing such substituent is isolated. 30

13. A process for preparing a compound according to Claim 1 wherein R and X are H, in which an alkali metal cyanide is reacted with one polyfluoroalkylidenimine of the formula



Z and Z' being as in Claim 1, where a compound is required having Z² and Z³ respectively identical with Z and Z', or the cyanide is reacted with more than one such polyalkylidenimine where a compound is required having Z² and/or Z³ different from Z and Z', to form a compound in which X is polyfluoromethylethylamino, from which this substituent is eliminated by heating. 35

14. A process according to Claim 13 in which the initially formed compound wherein X is polyfluoromethylethylamino is subsequently heated in the presence of a mineral acid to eliminate this substituent. 40

15. A process for preparing a compound according to Claim 1 wherein R and/or X is other than H in which a compound wherein R and X are H is prepared by a process according to Claim 13 or 14, and such compound or an alkali metal salt thereof is reacted with a hydrocarbylating agent, substituted hydrocarbylating or acylating agent. 45

16. A modification of the process according to Claim 15 in which a compound in which R and X are H is reacted with oxalyl chloride to form a 4-isocyanato compound which is thereafter reduced to form a compound wherein R is H and X is methyl. 50

17. A process according to any of Claims 12 to 15 in which the polyfluoroalkylidenimine is hexafluoroisopropylidenimine.

18. A process according to any of Claims 13 to 15 in which the polyfluoroalkylidenimine is pentafluoroisopropylidenimine. 55

19. A process for preparing a nitrogen heterocyclic compound as defined in Claim 1 substantially as described in any of Examples 1 to 39 herein.



20. A nitrogen heterocyclic compound prepared by a process according to Claim 19.

21. A pharmaceutical composition containing as active ingredient a compound according to Claim 1 or 20 and a nontoxic pharmaceutical carrier.

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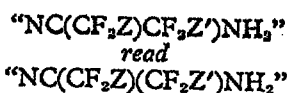
Index

Int. Cl.

ERRATA

SPECIFICATION No. 1,147,541

Page 4, First Formula drawing: for

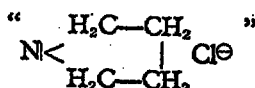


Page 6, line 51, for "Z'=Z=H" read
"Z'=Z=H"

Page 9, line 44, for "CdCl₂" read "CDCl₃"

Page 12, line 44, Formula drawing: after
"HNCH₂" insert "OH"

Page 14, line 9, for existing formula read



Page 16, line 27, after "Z'" insert "="

THE PATENT OFFICE
19th May, 1969

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* C L M S *