Anal. Calcd for $C_{13}H_{14}ClNO_3$: C, 56.47; H, 5.42; N, 4.70. Found: C, 56.74; H, 5.41; N, 4.79.

3-Methyl-4-(6-methyl-2-pyridyl)carbamoylpyrazole (18).—A solution of 9.5 g (0.03 mol) of **10** and 5 g (0.1 mol) of hydrazine hydrate in 100 ml of ethanol was refluxed for 3 hr. It was then poured into water and the solution was acidified with acetic acid. The precipitated crystals were recrystallized from ethanol, 4 g (62%), mp 236–239°.

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.60; N, 25.91. Found: C, 61.33; H, 5.57; N, 25.75.

3-Acetyl-5-carbo-*t*-butoxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridone (22b) (Table IV).—To a slurry of 26.7 g (0.1 mol) of **21** and 25 g (0.158 mol) of *t*-butyl acetoacetate in ice-cooled ethanol (150 ml), 6 g of $NaOCH_3$ (0.11 mol) was added. The solution became almost clear before the product crystallized. After 2 hr in an ice bath, the mixture was filtered and the product was washed with ethanol, yield 25 g.

3-Acetyl-5-carboxy-1-(*p*-chlorophenyl)-6-methyl-2-pyridione (22d) (Table IV).—Compound **22b** (20 g, 0.055 mol) was dissolved in 100 ml of concentrated H_2SO_4 by heating the mixture to 60°, whereupon it was left to stand at room temperature for 30 min. The solution was poured into ice water and filtered. The product was recrystallized from methanol–water, yield 14 g.

1-(*p*-Chlorophenyl)-3,5-diacetyl-6-hydroxy-2-pyridone (20). 1.—A slurry of 44 g (0.112 mol) of **8** in 400 ml of Clorox and 80 g of 50% aqueous NaOH was heated on a steam bath for 2 hr. Most of the starting material dissolved. The mixture was then cooled by addition of ice and acidified with concentrated HCl. The product was filtered off and recrystallized from ethanol, yield 10 g (29%), mp 238–240° dec.

2.—Compound **22a** (20 g, 0.06 mol) was added to a solution of 70 ml of methanol, 50 ml of water, and 30 g of 50% aqueous NaOH. The mixture was heated gently until the solid was dissolved and then left standing overnight. The product was filtered after acidification with concentrated HCl and recrystallized from ethanol, yield 15 g (82%).

Anal. Calcd for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.56. Found: C, 58.68; H, 4.10; N, 4.40.

Registry No.—**2**, 23600-24-0; **3**, 16867-47-3; **4**, 23646-59-5; **5**, 23600-26-2; **6**, 23600-27-3; **7**, 23600-28-4; **8**, 23646-60-8; **9**, 23600-29-5; **10**, 23600-30-8; **12**, 23646-61-9; **16**, 23600-31-9; **17**, 23600-32-0; **18**, 23600-33-1; **19**, 23646-64-2; **20**, 23600-34-2; **21**, 23600-35-3; **22a**, 23600-36-4; **22b**, 23600-37-5; **22c**, 23600-38-6; **22d**, 23600-39-7; **28**, 23600-40-0; **29**, 23646-62-0; **30**, 23646-63-1; **31**, 23674-48-8; **32**, 23600-41-1; **33**, 23600-42-2.

Acknowledgment.—We gratefully acknowledge the encouragement of this work by Dr. Charles L. Levesque.

Fluorinated Aminoimidazolines. Synthesis and Determination of Tautomeric Structure

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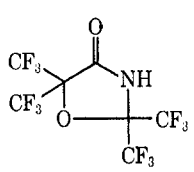
Hexafluoroacetone imine reacts with sodium cyanide to give 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), a compound that possesses pronounced pharmacological activity as a central nervous system depressant and muscle relaxant. This imidazoline has unexpected chemical and thermal stability. The ^1H nmr spectrum of ^{15}N-labeled **2** shows that it exists primarily as the amino tautomer, and not as the imino tautomer **16**, and indicates restricted rotation for the amino group because of the contribution of ionic resonance form **17** or solvent complexing. The preparation of several analogs, including 4-amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (**9**), 4-amino-2,2,5,5-tetramethyl-3-imidazoline (**12**), and 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**13**), is also described.

In earlier studies aimed at the synthesis of heterocyclic compounds highly substituted with fluoroalkyl groups, it was found that sodium cyanide reacts with 2 equiv of hexafluoroacetone to yield the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidinone



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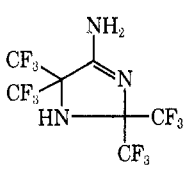
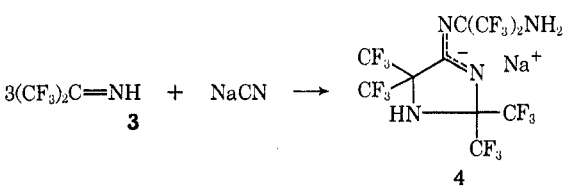


2

(**1**).[1] In continuing these studies, we have investigated the related reactions of cyanide with imines of fluoro ketones in attempts to prepare analogous heterocyclic compounds containing more nitrogen. One of the compounds that resulted from this study, 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**2**), has been shown in laboratory and clinical studies to possess pronounced pharmacological activity as a central nervous system depressant and muscle relaxant.[2]

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **32**, 951 (1967).

Reactions of Cyanide with Fluoro Ketone Imines.—Hexafluoroacetone imine (**3**) reacts readily and exothermally with a suspension of sodium cyanide in a polar solvent such as dimethyl sulfoxide, dimethylformamide, or acetonitrile at temperatures as low as −30° to give the 3:1 adduct **4**. Regardless of which reagent is in excess or the mode of addition, the 3:1 adduct is always formed.

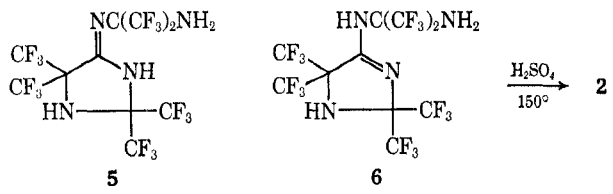


3 **4**

This behavior is in contrast to the reaction of hexafluoroacetone with sodium cyanide, which could be stopped at either a 1:1 adduct or a 2:1 adduct and which never formed a 3:1 adduct.[1] Acidification of **4**

(2) J. L. Claghorn and J. D. Schoolar, *Current Therap. Res.*, **10**, 279 (1968); I. M. Levine, P. B. Jossmann, D. F. Friend, and J. DeAngelis, *Clin. Pharmacol. Therap.*, **9**, 448 (1968); R. Clark, T. E. Lynes, W. A. Price, J. P. Marvel, D. H. Smith, and V. G. Vernier, *The Pharmacologist*, **10**, 197 (1968).

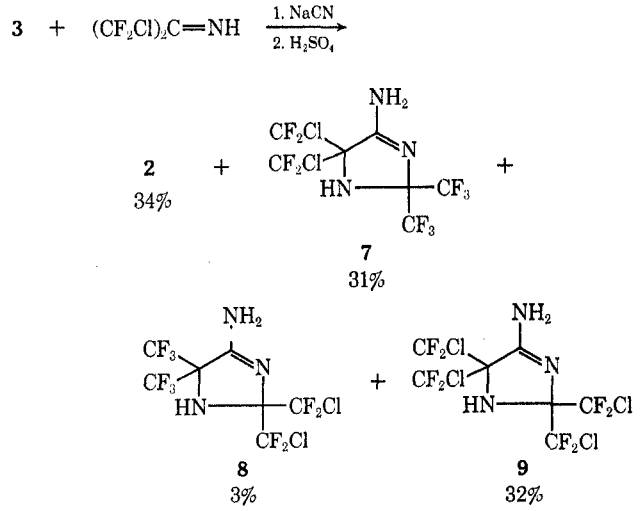
gave an easily sublimable heterocycle. Although two different tautomeric structures (**5** and **6**) can be written for this compound, the imidazoline structure **6** has been tentatively assigned on the basis of analogy to related compounds to be described later in this and a following paper.[3]



5 **6**

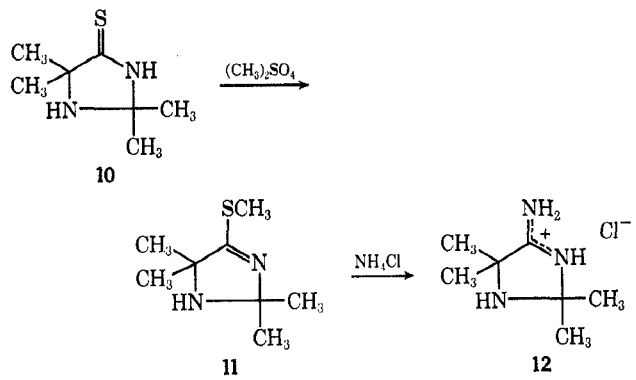
One unit of imine can be removed from **6**, either by pyrolysis or hydrolysis with concentrated sulfuric acid at 150°. The resulting aminoimidazoline **2** possesses exceptional thermal, hydrolytic, oxidative, and other chemical stability. Examples of this stability follow. (1) **2** can be dissolved in hot (150°) concentrated sulfuric acid or 20% oleum and recovered unchanged after dilution with water. No salt formation occurs in aqueous solutions with acids. (2) **2** is inert to oxidizing reagents such as chlorine, bromine, hydrogen peroxide, and peracids, and hypochlorites even at 100°. (3) **2** will not react with anhydrous hydrazine, even when held at reflux temperature for several days. (4) **2** shows remarkable thermal stability, even up to 500°. At higher temperatures, it can be pyrolyzed to CF_3CN, CHF_3, and C_2F_6.

Other similar 4-aminoimidazolines were prepared by the reaction of sodium cyanide with different imines, including the imines of chloropentafluoroacetone, 1,3-dichlorotetrafluoroacetone, pentafluoroacetone, and perfluorocyclopentanone (see Experimental Section). Imidazolines derived from two different imines were also prepared by adding sodium cyanide to a mixture of two fluoro ketone imines; all four possible imidazolines are formed, but not in the statistical proportion. For example, reaction of sodium cyanide with an equimolar mixture of 3 and $(CF_2Cl)_2C{=}NH$ gave imidazolines **2**, **7**, **8**, and **9** in the ratio 34:31:3:32, respectively.



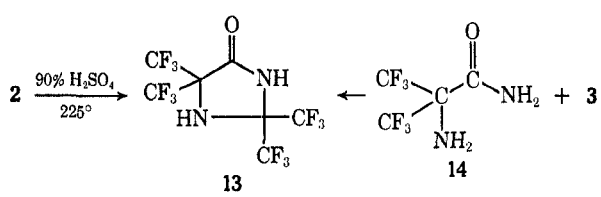
These imidazolines were separated by distillation and subsequent hydrolysis of their corresponding isocyanate derivatives,[3] which were formed by treatment of the imidazoline mixture with oxalyl chloride. Other mixed imidazolines were also prepared from **3** and $CF_3C(=NH)CF_2Cl$ and from **3** and $CF_3C(=NH)CF_2H$. In all cases, the isomer which contained the *gem*-trifluoromethyl groups on the 2-carbon position of the ring predominated (see Experimental Section).

The nonfluorinated analog of **2** could not be prepared by this method, since acetone imine is not stable. However, it was prepared and isolated as the hydrochloride salt (**12**) by reaction of the thio ether **11** with ammonium chloride. The thio ether was prepared by alkylation of the known thiolactam **10**[4] with methyl sulfate. This imidazoline possesses drastically different properties than **2** in that it forms salts with acids, is easily oxidized and hydrolyzed, and is thermally unstable.



10 **11** **12**

Structure Proof for 2.—The surprising inertness of **2** is consistent with its reported low toxicity when used as a pharmaceutical agent,[2] since hydrolysis or other degradation could lead to toxic materials such as fluoride ions. However, this inertness tends to cast doubt on the assigned structure. For this reason, a detailed study of the structure was undertaken. A proof of the skeletal structure was accomplished by the conversion of **2** into the lactam **13** by extremely vigorous hydrolysis with 90% sulfuric acid at 225°. The lactam **13** was independently synthesized by the condensation of hexafluoroacetone imine (**3**) with the amino amide **14**.



13 **14**

The ^{19}F nmr spectrum is also in agreement with the assigned structure **2**. Two signals of equal area were observed, each split into septets by *ca.* 5 Hz. Since the spin–spin coupled fluorine atoms are six bonds apart, this relatively large coupling constant may indicate a through-space interaction. This observed coupling constant is believed to be an average value between those of the *cis*- and the *trans*-trifluoromethyl groups; so the spectrum appears as an A_6X_6 pattern instead of the expected $A_3A'_3X_3X'_3$ pattern.

The higher field septets of both **2** and **13** are assigned so the trifluoromethyl groups in the 2 position, consistent with earlier observations that *gem*-trifluoromethyl groups flanked by N and/or O consistently

(3) W. J. Middleton, D. M. Gale, D. W. Wiley, and C. G. Krespan, *J. Org. Chem.*, **35**, 1485 (1970).

(4) J. C. Christian, *ibid.*, **22**, 396 (1957).

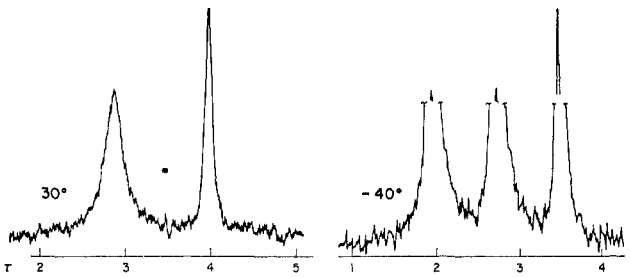
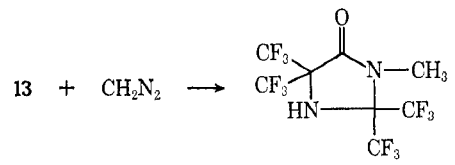


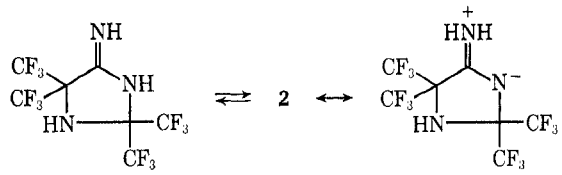
Figure 1.—Proton magnetic resonance spectra at 60 MHz of **2** at 30 and −40° in acetone-d_6.

appear at higher field than those attached to only one such atom in otherwise similar situations.[5] For example, the resonance for $(CF_3)_2C(NH_2)_2$ is 8.7 ppm higher field than that of amino amide **14**. This assignment is also supported by the ^1H–^{19}F spin–spin coupling observed between the methyl group and the higher field trifluoromethyl groups of methyllactam **15**, which was prepared by the action of diazomethane on **13**.



15

Tautomeric Determination.—It is possible to write another tautomeric structure (**16**) for **2** in which the double bond is shifted to an exocyclic position.



16 **17**

Attempts to prove by classical methods which of these two tautomeric structures best represents the compound were indecisive. In alkylation experiments, derivatives of both forms (**2** and **16**) that would be incapable of tautomerization could be prepared,[3] but the spectral and chemical properties of these derivatives were too similar to allow an assignment by analogy of an *exo* or an *endo* double bond to the parent. However, a detailed study of the proton nmr spectra of **2** did allow a definite tautomeric assignment to be made.

At temperatures above 25° in solvents or in the melt, the ^1H nmr spectrum of **2** shows two broad absorptions in the ratio of 2:1 (Figure 1). The protons causing the larger, lower field absorption exchanged rapidly with D_2O, whereas the sharper, higher field peak remained in the presence of D_2O until an acid was added. This spectrum does not differentiate between structures **2** and **16** (or an equilibrium mixture), for the larger peak could either be due to the amino group of **2** or be an exchange-averaged peak owing to H-3 and the imino H in structure **16**.

At lower temperature the lower field peak splits into two distinct peaks of equal area about 46 Hz apart

(5) See, *e.g.*, W. J. Middleton and/or C. G. Krespan, *et al.*, *J. Org. Chem.*, **30**, 1398, 1402 (1965); **32**, 948, 951 (1967); **33**, 1002 (1968); *J. Amer. Chem. Soc.*, **86**, 4948 (1964); **88**, 3617 (1966); **90**, 6813 (1968).

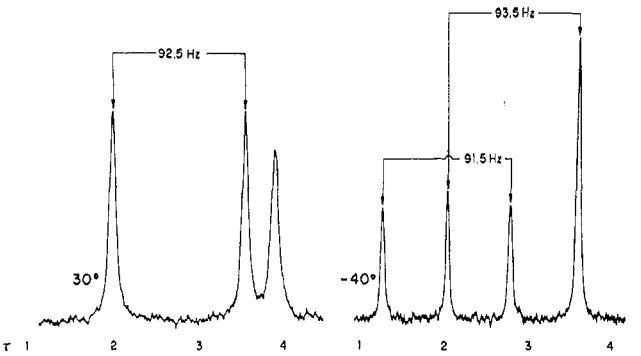


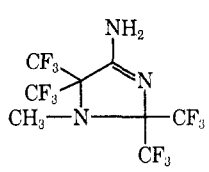
Figure 2.—Proton magnetic resonance spectra at 60 MHz of 4-(^{15}N-amino)-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline at 30 and −40° in acetone-d_6.

(Figure 1). Again, this result could be explained on the basis of either structure. If **16** were correct, the cooling could have slowed down the exchange rate so that averaging no longer occurred. If structure **2** were correct, restricted rotation about the exocyclic carbon–nitrogen bond due to a contribution of resonance from **17** (similar to that observed for amides) would be implied.

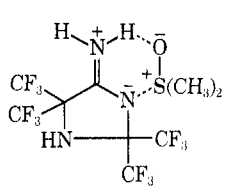
By observing the spin–spin coupling between nitrogen and hydrogen, this problem was resolved. Unfortunately, ^{14}N–^1H coupling is difficult to observe because of the quadrupole associated with ^{14}N. Isotropic ^{15}N has no quadrupole, however, and furthermore has a spin of $^1/_2$ (like ^1H). For the purpose of observing the ^1H nmr spectrum, **2** containing a ^{15}N label was prepared from ^{15}N-labeled sodium cyanide.

The labeled sample incorporated the ^{15}N exclusively as the exocyclic nitrogen, as shown by its complete loss when the sample was hydrolyzed to the lactam **13**. No scrambling of the ^{15}N occurred between the exocyclic nitrogen and the ring nitrogen in the 3 position, as would have been expected if a rearrangement similar to the Chapman rearrangement observed in the reaction of sodium cyanide with hexafluoroacetone[1] had occurred. This lack of rearrangement may reflect the fact that there is no driving force to form a more stable anion as there is in the case of the hexafluoroacetone reaction.

In the 30° ^1H nmr spectrum of the labeled sample of **2** (Figure 2), a sharp doublet (J_{NH} = 92.5 Hz, measured at both 60 and 40 MHz) now appeared in the place of the broad signal of the two easily exchangeable hydrogens. In the spectrum at −40°, this doublet became two doublets (J_{NH} = 91.5 and *ca.* 93.5 Hz). The coupling constant of the later doublet could not be measured exactly because the high-field leg overlapped the signal of the H in the 1-ring position. To remove this complication, the ^{15}N-labeled 1-methyl derivative **18**



18



19

was prepared[3] and its spectra were recorded at 25 and −40° (Figure 3).

The spectrum of **18** at 30° showed a single doublet (J_{NH} = 93.5 Hz) and at −40° two doublets (J_{NH} = 94.0 and 89.5 Hz). These spectra of the ^{15}N-labeled compounds clearly show that both of the easily exchangeable hydrogens in **2** and **18** are directly bound to the ^{15}N, since the coupling constants are large and are consistent with values to be expected for directly bound hydrogens.[6] Imino structures such as **16** are therefore eliminated, since the NH coupling would be expected to have a low value for the hydrogen not directly bound to ^{15}N in this structure.

The two separately observable peaks for the amino group in the low-temperature spectra of **2** must therefore result from restricted rotation about the C–N bond due to a contribution of ionic resonance from **17**. The observed values of the coupling constants indicate a large amount of s character in the hybridization of the NH bonds (closer to sp^2 than sp^3),[6] consistent with structure **17**.

The temperature necessary to cause the appearance of the two separate peaks appears to vary with solvent polarity. In dimethyl sulfoxide, the most polar solvent examined, the two peaks appeared at 10°. The formation of a complex such as **19** could aid in causing the restricted rotation. This conclusion was supported by the isolation of a stable 1:1 complex of **2** with dimethyl sulfoxide that could be recrystallized from benzene.

Experimental Section[7]

4-[1-Amino-2,2,2-trifluoro-1-(trifluoromethyl)ethylamino]-2,-2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (6).—Hexafluoroacetone imine (**3**), 20 ml (*ca.* 30.8 g, 0.187 mol), at −10°, was slowly distilled into a stirred suspension of 3.06 g (0.0625 mol) 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°. At the end of the addition (20 min being required) the reaction mixture became homogenous. The mixture was cooled to 20° and then poured into 500 ml of water containing 100 ml of aqueous 10% hydrochloric acid. The aqueous phase was decanted from the oil that separated, and the oil was washed with water until it solidified. This solid was collected on a filter, pressed dry, and then dried in a vacuum desiccator over P_2O_5, crude yield 24.1 g (74%). Recrystallization from pentane gave **6** as colorless prisms: mp 45–46°; ^{19}F nmr ($CDCl_3$) δ 72.8 (septet, 6 F, J_{HF} = 5 Hz), 77.9 (septet, 6 F, J_{HF} = 5 Hz), and 79.8 ppm (s, 6 F); ^1H nmr ($CDCl_3$) τ 4.5 (broad singlet, 1 H), 6.43 (broad singlet, 1 H), and 6.92 ppm (s, 2 H); ir (KBr) 5.97 μ (C=N).

Anal. Calcd for $C_{10}H_4F_{18}N_4$: C, 23.00; H, 0.77; F, 64.49. Found: C, 23.21; H, 0.91; F, 65.23.

4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (2).—A 47.1-g sample of **6** was dissolved in 100 ml of concentrated sulfuric acid, and the stirred solution was heated slowly to 150° and held at that temperature for 10 min. Frothing occurred during the heating period. The solution was cooled to 20° and poured over 1 l. of crushed ice. The white solid that formed was collected on a filter after the ice melted and was washed with water. Recrystallization from alcohol–water (1:2) gave 31.5 g (98%) of **2** as long, colorless needles: mp 159.7–160.4°; bp 194° (760 mm); ir (KBr) 5.90 μ (C=N); ^{19}F nmr (acetone) δ 71.5 (septet, 6 F, J_{HF} = 4.7 Hz) and 76.5 ppm (septet, 6 F, J_{HF} = 4.7 Hz); ^1H nmr (dimethyl sulfoxide-d_6) τ 2.80 (broad singlet, 2 H) and 3.94 (sharper singlet, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 357 (0.13), 338 (4.8), 288 (100), 219 (46), 173 (11), and 69 (30). Neutralization equivalents were determined by titration with tetra-*n*-butylammonium hydroxide in pyridine.

Anal. Calcd for $C_7H_3F_{12}N_3$: C, 23.55; H, 0.85; F, 63.85; N, 11.77; neut equiv, 357. Found: C, 23.72; H, 10.03; F, 63.86; N, 11.99; neut equiv, 356.7, 352.3, 351,3.

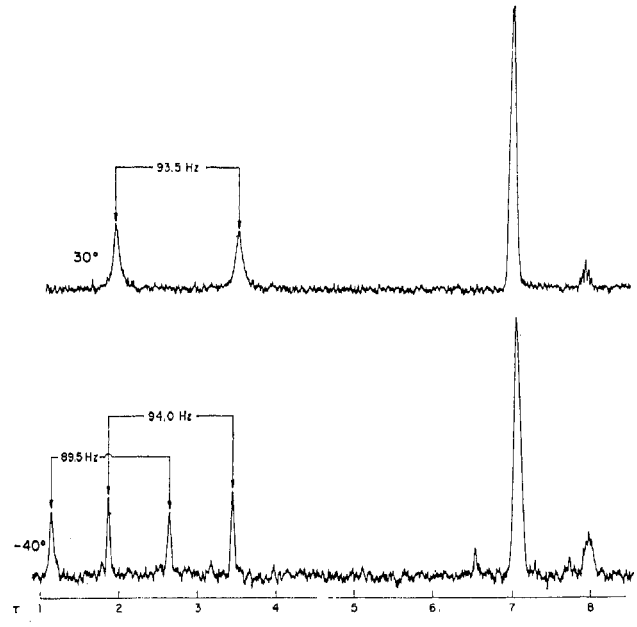


Figure 3.—Proton magnetic resonace spectra at 60 MHz of **18** at 30 and −40° in acetone-d_6.

4-Amino-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline (9).—Powdered sodium cyanide, 11.8 g (0.24 mol), was added portionwise over 15 min to a stirred solution of 47.5 g (0.24 mol) of 1,3-dichlorotetrafluoroacetone imine in 80 ml of dimethylformamide cooled to 0°. As the addition proceeded, the reaction mixture warmed slightly, and the rate of addition was adjusted so that the temperature remained below 10°. After the addition, the reaction mixture was poured into 200 ml of aqueous 10% hydrochloric acid, and the oil that separated was washed with water and dissolved in 50 ml of fuming sulfuric acid (20% SO_3). The sulfuric acid solution was heated to 150°, cooled, and poured over 200 ml of crushed ice. The solid that formed was collected on a filter, washed with water, and dried in air. Sublimation at 150° (0.5 mm) gave 26.5 g (78%) of **9** as a crystalline solid: mp 126–133°; ^{19}F nmr (acetone) δ 53.5 (m, 2 F), 55.1 (m, 2 F), 58.3 (m, 2 F), and 58.8 ppm (m, 2 F); ^1H nmr (acetone-d_6) τ 4.09 (1 H) and 2.9 ppm (2 H); ir (KBr) 5.94 μ (C=N).

Anal. Calcd for $C_7H_3Cl_4F_8N_3$: C, 19.87; H, 0.72; Cl, 33.53; F, 35.93; N, 9.84. Found: C, 20.22; H, 0.89; Cl, 33.85; F, 35.91; N, 9.61.

4-Amino-2,5-bis(chlorodifluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline.—This compound was prepared in 70% yield by a procedure similar to that used to prepare **9**, except that chloropentafluoroacetone imine was used in place of the dichloroimine, and was obtained as a white, crystalline powder: mp 120–122° (sealed capillary); ^{19}F nmr (acetone) δ 57.3 (m, 2 F), 62.1 (m, 2 F), 69.7 (m, 3 F) and 73.9 ppm (m, 3 F); ^1H nmr (acetone-d_6) τ 4.09 (1 H) and 2.9 ppm (2 H); ir (KBr) 5.94 μ (C=N).

Anal. Calcd for $C_7H_3Cl_2F_{10}N_3$: C, 21.56; H, 0.77; Cl, 18.18; F, 48.72; N, 10.77. Found: C, 21.94; H, 0.98; Cl, 18.03; F, 48.71; N, 10.79.

12-Amino-6H-hexadecafluoro-6,13-diazadispiro[4.1.4.2]tridec-12-ene.—This compound was prepared in 70% yield by a procedure similar to that used to prepare **9**, except that perfluorocyclopentanone imine was used in place of the dichloroimine, and was obtained as a white, crystalline powder: mp 168–171° (sealed capillary); ir (KBr) 5.92 (C=N) and 6.23 μ (NH_2); ^{19}F nmr (acetone-d_6) δ 120–140 ppm (m); ^1H nmr (acetone-d_6) τ 3.03 (NH_2) and 4.43 ppm (NH).

4-Amino-2,5-bis(difluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline (20).—This compound was prepared by a procedure similar to that used to prepare **9**, except that pentafluoroacetone

(6) G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 5564 (1964).

(7) Proton nmr spectra were obtained with a Varian A-60 spectrometer. Peak center positions are reported as τ values in parts per million. Fluorine nmr spectra were obtained with a Varian A56-60 spectrometer. Peak center positions are reported in parts per million upfield from $CFCl_3$ used as an internal reference.

imine[8] was used in place of the dichloroimine, and was obtained as a white, crystalline powder (mixture of two isomers): mp 142–144°; ^{19}F nmr (acetone) δ 72.8 (m, 3 F), 77.1 and 77.7 (multiplets, total 3 F), 127.0 (m, 2 F), and 131.0 ppm (m, 2 F); ^1H nmr (acetone-d_6) δ 3.56 (t, 1 H), 3.98 (t, 1 H), 5.12 (broad, 1 H) and 3.0 ppm (very broad, 2 H); ir (KBr) 5.91 μ (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.

4-Amino-5,5-bis(chlorodifluoromethyl)-2,2-bis(trifluoromethyl)-3-imidazoline (7).—Powdered sodium cyanide, 6.53 g (0.133 mol), was added portionwise over 30 min to a stirred solution of 33.0 g (0.2 mol) of hexafluoroacetone imine and 39.6 g (0.2 mol) of 1,3-dichlorotetrafluoroimine in 150 ml of dimethylformamide cooled to −30°. The reaction mixture was stirred for 1 hr at −30°, warmed to 25°, and mixed with 200 ml of 10% hydrochloric acid. The organic layer was washed twice with water and then dissolved in 40 ml of fuming sulfuric acid (20% SO_3). The solution was heated to 150°, cooled, and poured over crushed ice. The solid that formed was collected on a filter, washed with water, dried, and sublimed at 150° (10 mm) to give 33.0 g (64% total yield) of a mixture of imidazolines (**2**, **7**, **8**, and **9**), mp 118–155°.

A solution of 30.0 g of this mixture in 100 g of oxalyl chloride was stirred at 25° for 3 days and then distilled. There was obtained 9.10 g of 4-isocyanato-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline,[3] 8.65 g of 4-isocyanato-2,2,5,5-tetrakis(chlorodifluoromethyl)-3-imidazoline,[3] and 9.02 g of 4-isocyanato-5,5-bis(chlorodifluoromethyl)-2,2-bis(trifluoromethyl)-3-imidazoline, bp 104–105° (8 mm), ir (liquid) 4.40 μ (NCO). The ^{19}F nmr spectrum of the latter imidazoline indicated that this sample also contained a minor amount (8–9%) of the isomeric 4-isocyanato-2,2-bis(chlorodifluoromethyl)-5,5-bis(trifluoromethyl)-3-imidazoline, for the sample had two absorptions in the CF_3 region: δ 76.0 (multiplet, relative area 91–92%) and 71.2 ppm (multiplet, relative area 8–9%).

Anal. Calcd for $C_8HCl_2F_{10}N_3O$: C, 23.10; H, 0.24; Cl, 17.05; F, 45.67. Found: C, 23.23; H, 0.57; Cl, 17.07; F, 45.37.

A 6-g sample of the dichloroisocyanate was mixed with 25 ml of concentrated sulfuric acid. Gas was evolved. Water, 2 ml, was added, and the solution was heated to 150°, cooled, and poured over 25 ml of crushed ice. The solid that formed was collected on a filter, washed with water, dried, and sublimed at 110° (10 mm) to give 5.25 g of **7** as a white, crystalline powder, mp 129–132° (sealed capillary), ir (KBr) 5.90 μ (C=N). The ^{19}F nmr spectrum in acetone indicated that the sample also contained 8–9% isomeric 4-amino-2,2-bis(chlorodifluoromethyl)-5,5-bis(trifluoromethyl)-3-imidazoline (**8**), because the sample had two absorptions in the CF_3 region: δ 76.2 (multiplet, 91–92%) and 71.1 ppm (multiplet, 8–9%).

Anal. Calcd for $C_7H_3Cl_2F_{10}N_3$: C, 21.56; H, 0.77; Cl, 18.18; F, 48.72; N, 10.77. Found: C, 20.98; H, 0.64; Cl, 18.01; F, 48.64; N, 10.67.

4-Amino-5- (and -2-) chlorodifluoromethyl)-2,2,5- (and- 2,5,5-)-tris(trifluoromethyl)-3-imidazoline.—A 69:31 mixture of these isomers was prepared and purified in a manner similar to that of **7** and **8**, using hexafluoroacetone imine and chloropentafluoroacetone imine as the starting imines. This mixture was obtained as a white solid, mp 124–128°. The ^{19}F nmr spectrum in acetone showed multiplets for CF_2Cl at δ 58.0 (69%) and 62.6 ppm (31%) and multiplets for at δ 72.0 and 76.7 (ratio 1:2, total area of CF_3 region, 69%) and 70.2 and 74.5 ppm (ratio 2:1, total area of CF_3 region, 31%).

Anal. Calcd for $C_7H_3ClF_{11}N_3$: C, 22.53; H, 0.81; Cl, 9.49; F, 55.95; N, 11.24. Found: C, 22.69; H, 0.82; Cl, 8.87; F, 55.92; N, 11.17.

4-Amino-2-(difluoromethyl)-2,5,5-tris(trifluoromethyl)-3-imidazoline (21) **and 4-Amino-5-(difluoromethyl)-2,2,5-tris(trifluoromethyl)-3-imidazoline** (22).—Sodium cyanide, 7.55 g (0.15 mol), was added portionwise to a solution of 16.5 ml (0.15 mol) of hexafluoroacetone imine and 22.0 g (0.15 mol) of pentafluoroacetone imine in 100 ml of dimethylformamide cooled to −30°. The addition required 30 min. The reaction mixture was stirred for 1 hr at 25° and then mixed with 300 ml of 5% hydrochloric acid. The oil that precipitated was separated, washed with water, and dissolved in 50 ml of fuming sulfuric acid. The acid solution was heated quickly to 150°, cooled, and poured over ice. The solid that formed was collected on a filter, washed with water, and sublimed at 100° (10 mm) to give 11.1 g of a mixture of imidazolines. Gas chromatographic analysis (fluorosilicone column) indicated that this mixture was composed of 25.2% **2**, 10.4% **22**, 57.6% **21**, and 4.9% **20**.

A 2.8-g sample of **21** was isolated by preparative gas chromatography: mp 142–144°; ^{19}F nmr (acetone) δ 72.8 (m, 3 F), 77.7 (m, 6 F), and 137.3 ppm (m, 2 F); ^1H nmr (acetone-d_6) τ 3.53 (triplet, J = 53 Hz, CF_2H), 2.88 (broad singlet, NH), and 4.53 ppm (broad singlet, NH_2).

Anal. Calcd for $C_7H_4F_{11}N_3$: C, 24.79; H, 1.19; F, 61.36; N, 12.39. Found: C, 24.39; H, 1.21; F, 61.53; N, 12.50.

A 0.33-g sample of **22** was isolated by preparative gas chromatography: mp 152–154°; ^{19}F nmr (acetone) δ 72.8 (m, 6 F), 77.5 (m, 3 F), and 135.3 ppm (m, 2 F).

Anal. Calcd for $C_7H_4F_{11}N_3$: C, 24.79; H, 1.19. Found: C, 24.47; H, 1.19.

2,2,5,5-Tetramethyl-4-methylthio-3-imidazoline (11).—Dimethyl sulfate, 31.5 g (0.25 mol), was added dropwise with vigorous stirring to a solution of 31.65 g (0.2 mol) of 2,2,5,5-tetramethylimidazolidine-4-thione[4] (**10**) in 200 ml of aqueous 5% sodium hydroxide at 25°. The temperature of the reaction mixture rose to 45° in 30 min. The reaction mixture was cooled and extracted with 200 ml of ether in three portions. The ether extracts were dried ($MgSO_4$) and distilled to give 24.1 g (68%) of **11** as a colorless liquid: bp 71–72° (8.8 mm); $n^{25}D$ 1.4878; ^1H nmr (neat) τ 7.61 (singlet, SCH_3), 8.74 (singlet, 2 CH_3), 8.67 (singlet, 2 CH_3), and 8.06 ppm (singlet, NH).

Anal. Calcd for $C_8H_{16}N_2S$: C, 55.77; H, 9.36; N, 16.26; S, 18.61. Found: C, 55.67; H, 9.49; N, 16.27; S, 18.72.

A higher boiling fraction, bp 72–78° (8.8 mm), was redistilled to give 2.3 g of 1,2,2,5,5-pentamethyl-4-methylthio-3-imidazoline as a colorless liquid: bp 79–80° (8.7 mm); $n^{25}D$ 1.4927; ^1H nmr (neat) τ 7.66 (singlet, CH_3), 7.74 (singlet, CH_3), 8.79 (singlet, 2 CH_3), and 8.86 ppm (singlet, 2 CH_3).

Anal. Calcd for $C_9H_{18}N_2S$: C, 58.04; H, 9.74; N, 15.04; S, 17.21. Found: C, 57.76; H, 9.76; N, 15.02; S, 17.46.

4-Amino-2,2,5,5-tetramethyl-3-imidazoline Hydrochloride (12). A stirred mixture of 17.2 g (0.1 mol) of 2,2,5,5-tetramethyl-4-methylthio-3-imidazoline, 5.89 g (0.11 mol) of powdered ammonium chloride, and 100 ml of ethanol was heated at reflux for 14 days. During this time, methanethiol was slowly evolved. An additional 100 ml of ethanol was added, and the mixture was filtered while hot. The filtrate was cooled, and the solid that separated was collected on a filter, washed with ether, and recrystallized five times from ethanol to remove unreacted ammonium chloride. There was obtained 9.8 g of **12** as colorless crystals: mp 162–165° dec; ir (KBr) 5.89 μ (C=N); ^1H nmr (D_2O) τ 8.471 (singlet, 2 CH_3), 8.472 (singlet, 2 CH_3), and 5.2 ppm (DOH, exchange peak, 4 H).

Anal. Calcd for $C_7H_{16}ClN_3$: C, 47.32; H, 9.08; Cl, 19.96; N, 23.65. Found: C, 47.11; H, 9.19; Cl, 20.18; N, 24.00.

Aminobis(trifluoromethyl)acetamide (14).[9]—A solution of 3.6 g of aminobis(trifluoromethyl)acetonitrile,[10] 1 ml of water, and 20 ml of concentrated sulfuric acid was allowed to stand at room temperature for 3 days and then poured into 50 g of ice. The solution was extracted three times with 50-ml portions of ether, and the ether extracts were combined and dried ($MgSO_4$). Evaporation of the ether gave 2.2 g (56%) of the amide **14** as a colorless solid: mp 58–59°; ^{19}F nmr (acetone) 75.0 ppm (singlet); ^1H nmr (acetone-d_6) τ 2.63 (singlet, NH_2) and 7.04 ppm (singlet, NH_2).

Anal. Calcd for $C_4H_4F_6N_2O$: C, 22.87; H, 1.92; F, 54.26. Found: C, 23.18; H, 1.82; F, 53.73.

2,2,5,5-Tetrakis(trifluoromethyl)-4-imidazolidinone (13).—A mixture of 5.0 g (0.0238 mol) of aminobis(trifluoromethyl)-acetamide and 15 g (0.09 mol) of hexafluoroacetone imine was heated in a Hastelloy bomb at 150° for 12 hr. The bomb was cooled and vented, and nitrogen was bubbled through the liquid contents until they solidified. Sublimation of this solid at 100° (0.3 mm) gave 7.03 g (83%) of the imidazolidinone **13** as a crystalline, white powder: mp 107–108°; ir (KBr) 5.65 μ (C=O); ^{19}F nmr (acetone) δ 72.7 (septet, J = 4.5 Hz, 2 CF_3) and 78.1 ppm (septet, J = 4.5 Hz, 2 CF_3); ^1H nmr (acetone-d_6) τ 5.0 (singlet, NH) and 3.3 ppm (singlet, NH); mass spectrum (70 eV) m/e (rel intensity) 339 (0.14), 289 (72), 288 (56), 226 (47), and 69 (100).

Anal. Calcd for $C_7H_2F_{12}N_2O$: C, 23.47; H, 0.56; F, 63.67; N, 7.83. Found: C, 23.76; H, 0.91; F, 63.26; N, 7.50.

(8) W. J. Middleton, U. S. Patent, 3,342,864 (1967).

(9) We are indebted to Dr. D. M. Gale for this experiment.

(10) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

3-Methyl-2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (15).—A 3% solution of diazomethane in ether was added portionwise to a solution of 5.0 g of **13** in 10 ml of ether until nitrogen evolution ceased. The ether was evaporated under a stream of nitrogen, and the solid residue was recrystallized from alcohol to give 4.0 g of **15** as colorless crystals: mp 164–165° (sealed capillary); ir (KBr) 5.71 μ (C=O); ^{19}F nmr (acetone) δ 72.8 (septet, J = 4.4 Hz, 2 CF_3) and 75.3 ppm (septet, J_{FF} = 4.4 Hz, split further to quartets, J_{FH} = 0.9 Hz, 2 CF_3); ^{1}H nmr ($CDCl_3$) τ 6.83 (septet, J = 0.9 Hz, CH_3) and 3.25 ppm (singlet, NH).

Anal. Calcd for $C_8H_4F_{12}N_2O$: C, 25.82; H, 1.08; F, 61.27; N, 7.53. Found: C, 26.05; H, 1.30; F, 61.28; N, 7.81.

Hydrolysis of 4-Amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (2).—A solution of 100 g of **2** and 25 ml of water in 250 ml of concentrated sulfuric acid was heated at 225° in a sublimation apparatus for 5 days. The sublimate, most of which formed after the first day, was mixed with 200 ml of aqueous 5% sodium hydroxide. The solid that did not dissolve was collected on a filter and washed with water to give 5.8 g of unhydrolyzed **2**. The filtrate was made acidic with 10% hydrochloric acid, and the solid that precipitated was collected on a filter, washed with water, dried, and sublimed at 150° (5 mm) to give 33.2 g (33% conversion, 92% yield) of 2,2,5,5-tetrakis(trifluoromethyl)-4-imidazolidinone (**13**), identical by melting point and ir and nmr spectrum with an authentic sample. The sulfuric acid solution after cooling was poured over 1 l. of crushed ice and the solid that precipitated was collected on a filter, washed with water, and dried to give 58.0 g of unhydrolyzed **2**.

Dimethyl Sulfoxide Complex (19).—Dimethyl sulfoxide, 3.91 g (0.05 mol), was added to a solution of 17.86 g (0.05 mol) of **2** in 25 ml of ether. Heat was evolved, and a white solid precipitated. The solid was collected on a filter, dried in air (17.8 g), and recrystallized from benzene to give 15.7 g (72%) of the 1:1 complex as large, colorless prisms: mp 125–126°; ^{19}F nmr (acetone-d_6) δ 72.1 (septet, J = 5 Hz) and 76.7 ppm (septet, J = 5 Hz); ^{1}H nmr (acetone-d_6) τ 2.70 (NH_2), 3.72 (NH), and 7.42 ppm (singlet, 2 CH_3).

Anal. Calcd for $C_9H_9F_{12}N_3OS$: C, 24.83; H, 2.09; F, 52.39; N, 9.66; S, 7.37. Found: C, 25.18; H, 2.17; F, 52.15; N, 9.94; S, 7.47.

Pyrolysis of 2.[9]—Samples of **2** were pyrolyzed over quartz in a glpc–pyrolysis set-up from 200 to 650°. Little decomposition occurred below 500°; at 600° decomposition was moderate and at 750° it was complete. The products were isolated and shown to be a mixture of CF_3CN, CHF_3, and C_2F_6 by ir analysis.

^{15}N-Labeled 2.—A sample of **2** containing labeled nitrogen in the 4-amino group was prepared using ^{15}N-labeled (98.7%) sodium cyanide: mass spectrum (70 eV) *m/e* (rel intensity) 358 (0.1, parent − ^{15}N), 339 (5), 289 (100), 220 (47), and 69 (30). Hydrolysis of this sample with sulfuric acid gave the lactam **13**, which contained no ^{15}N as determined from its mass spectrum, which is identical with that of **13** prepared by other methods.

Registry No.—**2**, 23757-42-8; **2** (^{15}N labeled), 23758-03-4; **6**, 14372-88-4; **7**, 23757-44-0; **8**, 23757-45-1; **9**, 23757-46-2; **11**, 23757-47-3; **12**, 23757-48-4; **13**, 23757-49-5; **14**, 14316-86-0; **15**, 23829-37-0; **18**, 23757-51-9; **19**, 23757-52-0; **20**, 23757-53-1; **21**, 23757-96-2; **22**, 23757-97-3; 4-amino-2,5-bis(chlorodifluoromethyl)-2,5-bis(trifluoromethyl)-3-imidazoline, 23757-98-4; 2-amino-6H-hexadecafluoro-6,13-diazadispiro[4.1.4.2]tridec-12-ene, 23757-99-5; 4-amino-5-chloro(difluoromethyl)-2,2,5-tris(trifluoromethyl)-3-imidazoline, 23758-00-1; 4-amino-2-chloro(difluoromethyl)-2,5,5-tris(trifluoromethyl)-3-imidazoline, 23758-01-2; 1,2,2,5,5-pentamethyl-4-methylthio-3-imidazoline, 23758-02-3.

Fluorinated Aminoimidazolines. Reactivity of the Nitrogen Functions

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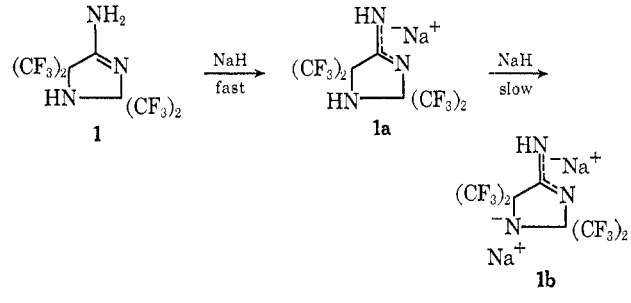
The very stable amino and amidino functions of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**1**) are attacked by strong acids and bases. Electrophilic alkylating agents such as dimethyl sulfate tend to attack at the 3 position, while nitration and acylation occur on the 4-amino group. Mono- and dianions stable at 25° can be prepared and used to react with **1** at the 1 position and on the 4-amino group. Appropriate combinations of these techniques allowed synthesis of all the nine possible methylated derivatives of **1**. The 4-nitramino and 4-isocyanato derivatives (**10** and **28**) are particularly useful intermediates.

The exceptional stability of 4-amino-2,2,5,5-tetrakis(polyfluoroalkyl)-3-imidazolines and their availability from fluorimines and cyanide ion[1] prompted a study of their properties. The discovery of the pronounced pharmacological activity of 4-amino-2,2,5,5-tetrakis(trifluoromethyl)-3-imidazoline (**1**) coupled with low toxicity[2] provided further incentive for a detailed investigation of the chemistry of these new fluorinated heterocycles.

Anion Formation with Strong Bases.—Although measurement of pH in protic systems established the near neutrality of **1**, the amidine function serves as a donor in the formation of strong hydrogen-bonded complexes with acceptors such as dimethyl sulfoxide and diethyl oxalate.[1] In aprotic media, salt formation with strong base does occur, so that monoanion **1a** forms easily with 1 equiv of sodium hydride–glyme or sodium methoxide–dimethyl sulfoxide.



Excess (threefold) sodium hydride and **1** in glyme formed **1a** at 25° and dianion **1b** at 60° or higher. Anion **1b** is stable at 25°, and **1b** is moderately stable at 84°

(1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **35**, 1480 (1970).

(2) The pharmacological studies on **1** as a skeletal muscle relaxant and central nervous system depressant are being reported separately. See I. M. Levine, P. B. Jossmann, D. G. Friend, and V. DeAngelis, *Chim. Pharmacol. Therap.*, **9**, 448 (1968); J. L. Claghorn and J. C. Schoolar, *Current Therap. Res.*, **10**, 279 (1968); R. Clark, T. E. Lynes, W. A. Price, J. P. Marvel, D. H. Smith, and V. G. Vernier, *The Pharmacologist*, **10**, 197 (1968).