Fluorinated Nitrogen Heterocycles *via* Cyclization. I. Trifluoromethyl-2-pyridones from Fluorinated 1,3-Dicarbonyls and Cyanoacetamide

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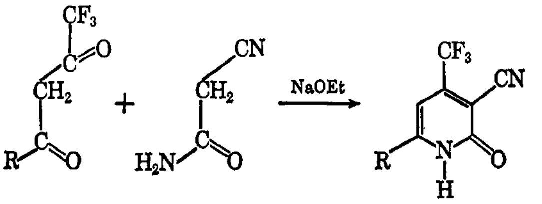
Fluorinated 1,3-dicarbonyl compounds having the general structure CF_3COCH_2COR undergo cyclization with cyanoacetamide in the presence of sodium ethoxide to give several new trifluoromethyl-2-pyridones. This synthesis provides a method for the preparation of fluorinated pyridine derivatives which are not readily prepared by the action of fluorinating agents on pyridine ring substituents. Spectral evidence is presented which indicates the isolation of two hydroxypyridone tautomers from the reaction of ethyl 4,4,4-trifluoroacetoacetate and cyanoacetamide.

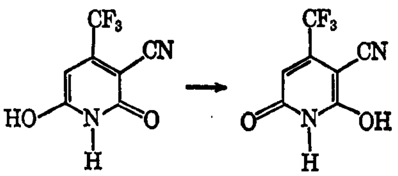
The preparation of fluorinated nitrogen heterocycles *via* cyclization of fluorinated intermediates has been sparsely reported in the literature except in the case of some pyrimidines.[1-3] Some fluoroalkylpyridines have recently been prepared *via* cyclization by a gas phase reaction at high temperatures,[4] but fluoroalkylpyridines, in general, are prepared by the action of fluorinating agents on chlorine-containing substituents on the pyridine ring.[5]

It has now been found that when the sodium salt of 2-cyanoacetamide reacts with fluorinated 1,3-dicarbonyls, having the general structure CF_3COCH_2COR, cyclizations occur giving trifluoromethyl-2-pyridones (I-IV).



I, R = CH_3
II, R = CF_3
III, R = C_6H_5
IV, R = 2-C_4H_3S
(2-thienyl)

When ethyl 4,4,4-trifluoroacetoacetate was used instead of a diketone, spectral evidence indicated that the hydroxypyridone product (Va) was isolated which gave rise to tautomer Vb (discussed below).



Va Vb

In those cases where the β-dicarbonyls were unsymmetrical, two positional isomers are possible in which the substituents in the 4 and 6 positions are interchanged. There is considerable evidence, however, which shows that the methylene group of cyanoacetamide tends to react with the more electrophilic and/or least hindered carbonyl.[6-12] Some exceptions have been reported, notably the direct reaction of certain sodium enolates with cyanoacetamide.[13] In the present case, because the trifluoromethyl group is strongly electron withdrawing and relatively small in bulk, the adjacent carbonyl carbon should be the more reactive positive center in the 1,3-diketone intermediate. Thus the trifluoromethyl substituent in compounds I, III, and IV should appear in the 4 position.

Recent attempts in this laboratory to prepare fluorinated pyridines *via* cyclization utilizing the Hantzsch reaction[14] were unsuccessful. 1,1,1-Trifluoro-2,4-pentanedione (trifluoroacetylacetone) was brought together in the cold with 36% formaldehyde, a catalytic quantity of diethylamine, and ammonia gas in an effort to synthesize 3,5-diacetyl-2,6-bis(trifluoromethyl)-1,4-dihydropyridine. The only product isolated was ammonium trifluoroacetate, formed apparently *via* hydrolysis of the trifluoroacetylacetone under the conditions of the experiment. It was subsequently found that ammonium trifluoroacetate could not be prepared by the slow addition of 30% ammonium hydroxide to cold trifluoroacetylacetone. A white product was isolated, however, which was shown not to be ammonium trifluoroacetate, but was not characterized further.

To prevent hydrolysis of the 1,3-diketone under Hantzsch conditions, the preparation of 3,5-diacetyl-4-(*n*-propyl)-2,6-bis(trifluoromethyl)-1,4-dihydropyridine was attempted under anhydrous conditions using anhydrous butyraldehyde. No fluorinated pyridine derivative was obtained. A product was isolated whose elemental analysis, and lack of carbonyl absorption in its infrared spectrum, indicated that it was probably 4-imino-5,5,5-trifluoro-2-penten-2-ol.

Spectral Interpretations.—The infrared and n.m.r. spectra of the product obtained by the reaction of ethyl 4,4,4-trifluoroacetoacetate and cyanoacetamide were studied, leading to formulation of product Va as a hydroxypyridone compound. It was found that the product first isolated undergoes tautomerization and that the tautomeric shift may be followed when the

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[2] E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3278 (1959).

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[13] R. K. Blackwood, G. B. Hess, C. E. Larrabee, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **80**, 6244 (1958).

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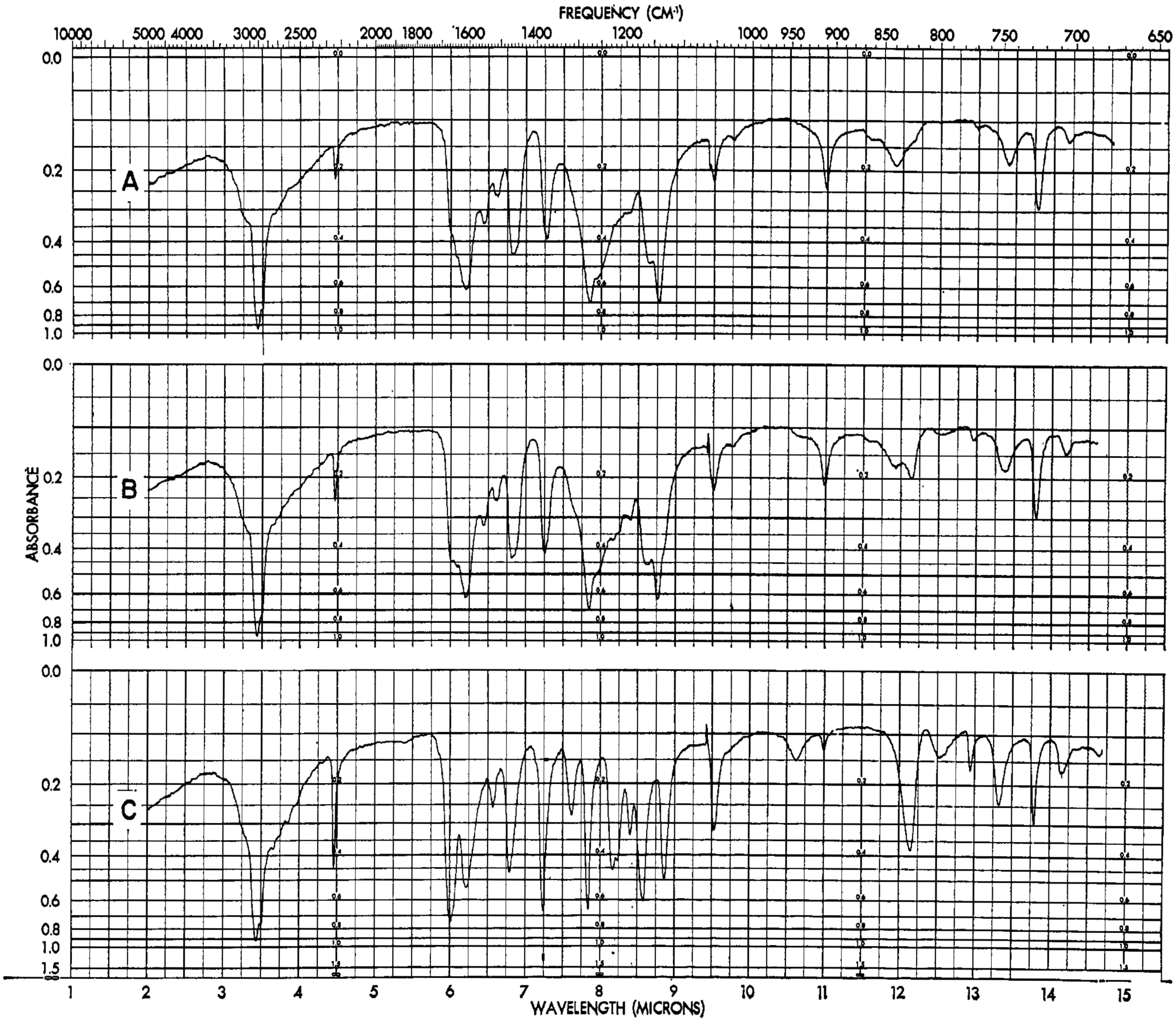
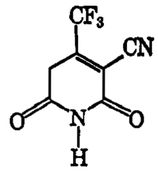


Figure 1.—Infrared spectral changes showing tautomeric shift of Va when placed (Nujol mull) in the beam of the spectrophotometer for a period of about 75 min.: A, initial run on Va; B, run after 35-min. time lapse; C, run after 75-min. time lapse showing conversion to Vb.

compound in the solid state (Nujol mull) is placed in the beam of the infrared spectrophotometer for a period of about 75 min.[15] Repeated runs throughout this period under these conditions produce many spectral changes (Figure 1).

The change of the shoulder at 1665 cm.$^{-1}$ into a strong band (Figure 1) indicates the presence of a carbonyl in both tautomeric forms. This precludes the possibility that the 2,6-dihydroxy compound is involved in the tautomerism. That carbonyl in 2-pyridone and derivatives absorbs strongly in the region 1650–1690 cm.$^{-1}$ has been reported by other workers.[16–18] The other compounds (I–IV) prepared in this work, as expected, also show strong absorptions in this region.



Vc

The possibility was also considered that the reaction product first isolated is the 2,6-diketo tautomer Vc, and that the spectral change in the 6-μ region indicates enolization of one of the carbonyls to give either Va or Vb.[19] This change involves disappearance of the shoulder at 1643 cm.$^{-1}$. This shoulder may be construed to be due to a second carbonyl. An inspection

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[15] Compound Va tautomerizes to Vb on standing for several months or when heated at 130° for about 15 hr. Vb can be reconverted to Va by recrystallizing from 15% hydrochloric acid and drying at 100° (30 mm.) for 2 hr.

[16] A. R. Katritzky and R. A. Jones, *J. Chem. Soc.*, 2947 (1960).

[17] Yu. N. Sheĭnker and V. M. Reznikov, *Dokl. Akad. Nauk SSSR*, **102**, 109 (1955); *Chem. Abstr.*, **49**, 12130 (1955).

[18] S. F. Mason, *J. Chem. Soc.*, 4874 (1957).

[19] The diketo tautomer, with the double bond between the 4 and 5 carbon atoms, was not considered likely since the double bond in the tautomer shown is conjugated with the nitrile substituent as well as with the carbonyl group.

of the n.m.r. spectra in deuterated acetone,[20] however, seems to rule out the diketo tautomer. Both reaction product and the tautomer to which it is converted (Va and Vb) show only two signals.[21] The n.m.r. spectrum of the initially found reaction product (Va) shows signals at 389 (sharp, 1H) and 655 c.p.s. (sharp, 2H).[22] This finding is only consonant with structures Va and Vb and is incompatible with the diketo form. The n.m.r. spectrum of the reaction product, after long standing (Vb), however, is different; a sharp signal appears at 372 (1H) and a broad signal at 592 c.p.s. (2H). This behavior also is in best accord with structures Va and Vb. Based on elemental and spectral analysis and the method of synthesis, Va and Vb appear to be the tautomers involved in the transformation.

It is difficult to discern hydroxyl absorption in the infrared spectra of hydroxypyridones because of the proximity of the N–H absorption in the 3–4-μ region. Both compounds (Va and Vb), however, give positive ferric chloride tests (light purple), which confirms the presence of hydroxyl. Although 2-pyridone itself gives a faint color test with ferric chloride, substituted 2-pyridones, such as compound I, and the model compounds 4-methyl-2(1H)-pyridone and 6-methyl-2(1H)-pyridone give no colors.

The fact that the tautomeric transformation involves the shift of Va to Vb and not Vb to Va is indicated by the strong increase in nitrile absorption intensity (Figure 1) at 2245 cm.$^{-1}$. It has been observed[23] that electron-withdrawing groups *ortho* or *para* to an aromatic nitrile group decrease the nitrile intensity. This has been attributed to a decrease in electron density on the carbon atom carrying the nitrile group. Others[24] have found, in the case of cyano-*s*-triazines, that the nitrile intensity is entirely quenched by the nitrogen atoms of the triazine ring. Sensi and Gallo[25] have also shown, in a study of 2-pyridone and 4-pyridone and their 1-methyl derivatives, that the base-weakening effect of the carbonyl is mostly inductive. Thus, in the present case, the compound showing the weaker nitrile absorption is assigned structure Va, in which carbonyl is the adjacent group, and the compound showing the stronger absorption is assigned structure Vb in which hydroxyl is the adjacent group. Similar low-intensity nitrile bands shown by compounds I–IV indicate the pyridone form.

The isolation of two tautomers of a pyridone-type compound has been reported in only one other case.[26]

The trifluoromethyl-2(1H)-pyridones prepared in this study all exhibited, as expected, strong C–F absorption bands in the region 1100–1330-cm.$^{-1}$. These compounds also gave broad bands in the 2400–3200-cm.$^{-1}$ region, which have been attributed by others to stretching of associated N–H[27] or to N–H and OH stretching frequencies.[28] A band (Nujol) at 3058 cm.$^{-1}$ attributed to the stretching vibration of the N–H linkage has been reported in the spectrum of 2-pyridone.[25] The compounds prepared in this study show similar absorptions.

Blue fluorescence in alcohol, water, and acetone under ultraviolet illumination is exhibited by all the compounds prepared. Compounds I and II give intense fluorescence in sunlight. There is evidence that the fluorescence exhibited by pyridone compounds may be related to the shift of the keto–enol equilibrium to the enol form. Only those compounds fluoresce, which are capable of being converted to the enol tautomer.[29–31]

Experimental Section[32]

3-Cyano-6-methyl-4-trifluoromethyl-2(1H)-pyridone (I).—Clean dry sodium metal (9.4 g., 0.41 g.-atom) was dissolved in 200 ml. of absolute alcohol. After the temperature of the solution had fallen to about 50°, cyanoacetamide (33.6 g., 0.40 mole) was added with stirring over a period of 0.5 hr., and the mixture was stirred for 1.5 hr. at 50–60°. 1,1,1-Trifluoro-2,4-pentanedione (61.6 g., 0.40 mole) was then added dropwise over a period of 0.5 hr., and the mixture was stirred for 13 hr. at 70°. After the addition of 150 ml. of water, the mixture was neutralized with 15% hydrochloric acid (about 50 ml.) and evaporated in an air stream until about 250 ml. of mixture remained. The resulting yellow-brown precipitate was removed by filtration under suction, and purification by several recrystallizations from chloroform gave white, powdery clusters (13.8 g., 17%), m.p. 232–234° dec., λ_{max} 237 and 355 mμ (ϵ 5600 and 10,900, respectively). Infrared bands appeared at 3035 sh[33] (N–H), 2236 w (CN), and 1668 vs cm.$^{-1}$ (C=O). Other bands were at 1626 s, 1555 m, 1497 m, 1419 m, 1349 s, 1054 s, 954 m-b, 888 w, 847 m, 780 vw, and 692 vw-b cm.$^{-1}$.

Anal. Calcd. for $C_8H_5F_3N_2O$: C, 47.53; H, 2.49; F, 28.20; N, 13.86. Found: C, 47.22; H, 2.64; F, 27.98; N, 14.01.

3-Cyano-4,6-bis(trifluoromethyl)-2(1H)-pyridone (II).—The reaction was performed initially in the same manner as above, employing 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (83.2 g., 0.40 mole) as the fluorinated intermediate. The mixture, however, was heated for a period of 8 hr. at 70–80°. After neutralization and concentration, the mixture was extracted several times with ether and the ether extracts were discarded.[34] Further concentration to a very small volume resulted in precipitation of the product as the sodium salt. Crystallization from 10% sodium hydroxide gave glittering, white leaflets. Recrystallization from ether gave white clusters, highly hygroscopic, m.p. 253–255° dec., giving intense blue fluorescence (sunlight) in water, alcohol, and acetone.

Anal. Calcd. for $C_8HF_6N_2NaO$: C, 34.55; H, 0.36; N, 10.08; Na, 8.27. Found: C, 35.08; H, 0.34; N, 10.20; Na, 8.26.

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(20) The n.m.r. spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.) at normal operating temperature (*ca.* 25–30°). Chemical shifts were measured in cycles per second (c.p.s.) from tetramethylsilane which was used as an internal standard.

(21) Vb is considerably more soluble in deuterated acetone than Va.

(22) Va does not tautomerize in acetone. It is recovered intact when recrystallized from a small volume of acetone and dried at 80° (50 mm.) for 1 hr.

(23) P. Sensi and G. G. Gallo, *Gazz. chim. ital.*, **85**, 224, 235 (1955); for a review of the variations in nitrile intensity in the infra-red of various nitrile compounds, see L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 265.

(24) E. C. Taylor and C. W. Jefford, *J. Am. Chem. Soc.*, **84**, 3744 (1962).

(25) P. Sensi and G. G. Gallo, *Ann. chim.* (Rome), **44**, 232 (1954); *Chem. Abstr.*, **49**, 14757 (1955).

(26) *Cf.* ref. 12, p. 624.

(27) H. Shindo, *Chem. Pharm. Bull.* (Tokyo), **7**, 407 (1959).

(28) R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, **78**, 2393 (1956).

(29) *Cf.* ref. 12, p. 694.

(30) O. Mumm, *Ber.*, **72B**, 29 (1939); *Chem. Abstr.*, **33**, 2808 (1939).

(31) U. Kubli and E. Schmid, *Helv. Chim. Acta*, **28**, 213 (1945); *Chem. Abstr.*, **40**, 4959 (1946).

(32) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer with samples run as Nujol mulls. Ultraviolet and visible spectra were determined in 1-cm. quartz cells using a Beckman Model DK-2A spectrophotometer with samples run in 95% alcohol.

(33) sh = shoulder, vs = very strong, s = strong, m = medium, w = weak, vw = very weak, b = broad.

(34) Prior to extraction with ether, an aliquot evaporated to dryness gave a solid which was purified by crystallizations from benzene containing a small amount of acetonitrile. This product, nonfluorescent, white needles, m.p. 271–272° dec., was not identified. Extraction with ether removes it and unreacted 1,1,1,5,5,5-hexafluoro-2,4-pentanedione.

The sodium salt was dissolved in a minimum of water and 5% hydrochloric acid was added dropwise until a precipitate formed.[35] The solution was then heated, and 5% hydrochloric acid was added dropwise until all material dissolved. Carbon black was added to the hot solution prior to filtration, and, upon cooling, the product crystallized out. Recrystallization from 5% hydrochloric acid gave white clusters (12.3 g., 12%): m.p. 119–121°; blue fluorescence in water, alcohol, and acetone[36]; λ_{max} 246, 314, and 362 mμ.[37] Infrared spectrum showed bands at 3060 s (N–H), 2245 w (CN), and 1670 vs cm.$^{-1}$ (C=O). Other bands appeared at 1634 s, 1592 m, 1568 m, 1501 m, 1412 w, (989, 984) s,[38] 928 w-b, 913 w, 887 m, 873 m, 783 vw, 748 vw, 743 m, 702 vw, and 692 w cm.$^{-1}$.

Anal. Calcd. for $C_8H_2F_6N_2O$: C, 37.52;. H, 0.79; F, 44.51; N, 10.94. Found: C, 37.79; H, 0.70; F, 45.65; N, 10.59.

3-Cyano-6-phenyl-4-trifluoromethyl-2(1H)-pyridone (III).—The reaction was carried out in the same manner as that for I, using 1,1,1-trifluoro-5-phenyl-2,4-pentanedione (86.5 g., 0.40 mole). The mixture, however, was heated for 16 hr. at 70° and then made strongly acidic with 15% hydrochloric acid (about pH of two). Several crystallizations of the product from alcohol gave yellow-green needles (31.0 g., 29%): m.p. 300–301°; λ_{max} 264, 342, and 376 mμ (ϵ 11,000, 10,200, and 13,200, respectively). Infrared bands were at 3060 sh (N–H), 2226 w (CN), and 1656 vs cm.$^{-1}$ (C=O). Other bands were at 1608 s, 1577 m, 1547 m, 1512 m, 1405 m, 1333 s, 1319 sh, 1068 m, 1033 vw-b, 998 vw, 975 m, 925 w, 881 w-b, 853 w, 769 m, 705 w, and 683 m cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_7F_3N_2O$: C, 59.09; H, 2.67; F, 21.57; N, 10.60. Found: C, 59.22; H, 3.06; F, 22.13; N, 11.06.

3-Cyano-6-(2-thienyl)-4-trifluoromethyl-2(1H)-pyridone (IV).—The reaction was performed in the same way as that for III, employing 1,1,1-trifluoro-5-(2-thienyl)-2,4-pentanedione. Several crystallizations of the product from alcohol gave yellow needles in 36% yield, m.p. 300–303° dec., λ_{max} 272 and 363 mμ (ϵ 7100 and 17,500, respectively). Infrared bands appeared at 3065 m (N–H), 2231 m (CN), and 1654 vs cm.$^{-1}$ (C=O). Other bands were at 1592 s, 1553 m, 1489 w, 1416 s, 1332 m, (1082, 1075) w,[38] 1047 m, 996 vw-b, 951 w, 945 w, 901 w-b, 861 m, 843 w, 830 w, 821 vw, 807 vw-b, 771 vw, 751 vw, 710 m, and 690 w cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_5F_3N_2OS$: C, 48.89; H, 1.86; F, 21.09; N, 10.37; S, 11.87. Found: C, 49.19; H, 2.18; F, 20.93; N, 10.58; S, 12.03.

3-Cyano-6-hydroxy-4-trifluoromethyl-2(1H)-pyridone (Va).—The reaction was carried out in a manner similar to that for III, using ethyl 4,4,4-trifluoroacetoacetate as the fluorinated intermediate. Several crystallizations of the product from 15% hydrochloric acid, using carbon black, gave the 1.5 hydrate in 26% yield, white needles, m.p. 243–246° dec. Drying in a vacuum oven at 100° (30 mm.) for 2 hr. resulted in a loss of water of 11.65% (theoretical loss of water is 11.69%) and gave the anhydrous product in the form of white needles,[39] λ_{max} 254 and 342 mμ (ϵ 12,400 and 16,200, respectively).

Anal. Calcd. for $C_7H_3F_3N_2O_2$: C, 41.19; H, 1.48; F, 27.92; N, 13.73. Found: C, 41.51; H, 1.67; F, 27.82; N, 13.61.

Compound Va, dissolved in a minimum of hot water and made slightly alkaline with 10% ammonia, gave the ammonium salt on standing. Recrystallization from acetonitrile using carbon black gave white clusters, m.p. 305–306° dec. (sealed capillary), with some sublimation occurring at about 265°.

Anal. Calcd. for $C_7H_2F_3N_2O_2 \cdot NH_4$: C, 38.02; H, 2.74; F, 25.77; N, 19.00. Found: C, 37.96; H, 2.39; F, 26.10; N, 19.09.

Attempted Preparation of 3,5-Diacetyl-2,6-bis(trifluoromethyl)-1,4-dihydropyridine.—To trifluoroacetylacetone (154.1 g., 1.0 mole), cooled in an ice–water bath, was added 36% aqueous formaldehyde (48.6 g., 0.59 mole) and 10 drops of diethylamine. The flask was kept cold for 6 hr., shaken occasionally, and then allowed to stand at room temperature for 42 hr. After 300 ml. of ether had been added, the mixture was dried over sodium sulfate, filtered, stripped of ether, and diluted with 200 ml. of absolute alcohol. The flask was cooled in an ice–water bath, and dry ammonia was bubbled through the mixture for 7.5 hr. After the open flask was allowed to stand in a hood at room temperature for 48 hr., excess alcohol was removed by distillation under vacuum of a water aspirator. An orange crystalline product was collected in a receiver immersed in an ice–water bath *via* distillation through a heated condenser at a pressure of approximately 2 mm. Crystallization from benzene containing a little acetone gave ammonium trifluoroacetate, white crystals, m.p. 120–123°. Its infrared spectrum was identical with the spectrum of the crystalline product formed by the reaction of ammonium hydroxide with trifluoroacetic acid.

Anal. Calcd. for $C_2H_4F_3NO_2$: C, 18.33; H, 3.07; F, 43.49; N, 10.69. Found: C, 19.33; H, 3.24; F, 43.44; N, 10.76.

Attempted Preparation of 3,5-Diacetyl-4-(*n*-propyl)-2,6-bis-(trifluoromethyl)-1,4-dihydropyridine.—The reaction was performed in the same way as that immediately above, employing dried and freshly distilled butyraldehyde (43.3 g., 0.60 mole). Several crystallizations of the product from water probably gave 4-imino-5,5,5-trifluoro-2-penten-2-ol, white platelets, m.p. 87–88°.

Anal. Calcd. for $C_5H_6F_7NO$: C, 39.22; H, 3.95; F, 37.23; N, 9.15. Found: C, 39.18; H, 3.79; F, 37.52; N, 9.08.

Acknowledgment.—The author is indebted to Dr. Charles W. Jefford of Temple University for the determination and interpretation of the n.m.r. spectra.

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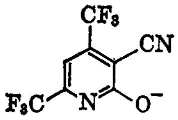
[35] An examination of the infrared spectrum of the sodium salt shows the absence of carbonyl which appears as a strong band at 1670 cm.$^{-1}$ in the keto tautomer (II). Compound II apparently exists in neutral aqueous solution as the water-soluble enolate ion (shown below). This also appears to be the case for mildly acidic solutions, since only when the reaction mixture is made highly acidic (pH of about 2 or below) can the compound be isolated as the 2-pyridone.



[36] The fluorescence in sunlight displayed by compound II in water solution is quenched at a pH of 2 or below. Compound I, however, does not behave in this manner.

[37] ϵ is not reported because of nonconformity to Beer's law.

[38] Doublet.

[39] Since high temperatures will convert Va to Vb, the melting point of the anhydrous product, 246–249° dec., with some sublimation occurring at approximately 225°, is that of compound Vb. The same transformation undoubtedly occurred during the determination of the melting point of the 1.5 hydrate.