

Studies on Organic Fluorine Compounds. V.¹⁾ Preparations and Reactions of N-Oxides of Trifluoromethylated Pyridines²⁾

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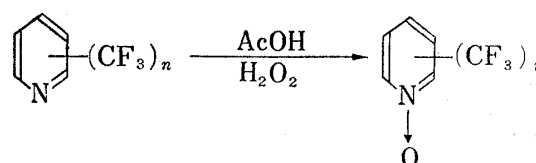
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First, N-oxidation of trifluoromethylated pyridines was carried out. The three isomers of trifluoromethylpyridine were successfully N-oxidized using acetic acid and hydrogen peroxide, but with 2,4- and 2,6-bis(trifluoromethyl)isomers of bis(trifluoromethyl)pyridine, N-oxidation was successful only when trifluoroacetic acid and hydrogen peroxide were used. Next, the reaction of the N-oxides of the three isomers of (trifluoromethyl)pyridine with acetic anhydride and their Reissert reaction were carried out; the effect of trifluoromethyl group was very marked. The success in the Reissert reaction with pyridine series is only second to that with 4-chloropyridine 1-oxide.

In the previous papers,⁴⁾ we reported that the syntheses of bis(trifluoromethyl)pyridines were carried out and that their infrared and mass spectra were studied, expecting the strongly electron-withdrawing trifluoromethyl group to show interesting behaviors, both chemically and physically. On the other hand, there is no report published on the effect of trifluoromethyl groups on the reactivity of the heterocycles possessing these groups. In this paper, we wish to report the results of an investigation on N-oxidation of some trifluoromethylated pyridines, the reaction of these N-oxides with acetic anhydride, and their reaction with benzoyl chloride and potassium cyanide.

Owing to the strong electron-withdrawing effect of trifluoromethyl group, pyridines with such a group do not easily form a hydrochloride. They were, therefore, assumed to resist N-oxidation by acetic acid and hydrogen peroxide, but, on heating in a boiling water bath for 10–15 hours, mono(trifluoromethyl)pyridines, all the three isomers, gave N-oxides in a good yield. The structure of these products was presumed from their elemental analyses, infrared (IR) spectra, and ultraviolet (UV) spectra, where the blue-shift appearing when solvents were changed from dioxan to ethanol confirmed our assumption. The fact that the shift is smaller than 20 mμ, which is unusual for N-oxides, can be attributed to the electron-withdrawing effect of trifluoromethyl groups which prevent N-oxides from making a hydrogen bonding with ethanol.

Secondly, N-oxidation of bis(trifluoromethyl)pyridines was carried out by heating them with acetic acid and hydrogen peroxide on a boiling water bath for 20 hours; 2,5-bis(trifluoromethyl) isomer was obtained only in 9% yield and unchanged material was recovered with



position of CF₃

n=1 n=2

I : 2 IV : 2, 5

II : 3 V : 2, 4

III : 4 VI : 2, 6

Chart 1

1) Part IV: Y. Kobayashi, C. Akashi, and K. Morinaga, *Chem. Pharm. Bull.* (Tokyo), **16**, 1784 (1968).

2) Most part of this work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.

3) Location: Kashiwagi 4-chome, Shinjuku-ku, Tokyo.

4) a) Y. Kobayashi and E. Chinen, *Chem. Pharm. Bull.* (Tokyo), **15**, 1896 (1967); b) Y. Kobayashi, F. Nakano, and E. Chinen, *ibid.*, **15**, 1901 (1967).

the 2,4-bis(trifluoromethyl) isomer. As this phenomenon seems to be due to the lower electron density of the nitrogen atom in 2,4-bis(trifluoromethyl) isomer than that in 2,5-bis(trifluoromethyl) isomer, N-oxidation was carried out with hydrogen peroxide and trifluoroacetic acid, whose acidity is stronger than acetic acid, and the desired substance was obtained in a fairly good yield.

This fact confirmed our expectation that the 2,4-bis(trifluoromethyl) isomer should be more resistant to N-oxidation than the 2,5-bis(trifluoromethyl) isomer, which is based on the results of mass spectrometry in our previous work. It has been found that, whereas trifluoromethyl groups on 2- and 4- positions readily leave the ring, those on 3- (or 5-) position do not. Similarly, an N-oxide was formed in a fairly good yield from the 2,6-bis(trifluoromethyl) isomer, when trifluoroacetic acid was used as a solvent.

Next, the reaction with acetic anhydride,⁵⁾ which is known to effect rearrangement of the N-oxide group, was carried out. On boiling trifluoromethylated pyridine N-oxides with acetic anhydride and treating the mixture with alkali, 6-pyridone⁶⁾ derivative was formed in a poor yield with 2-trifluoro isomer, while 2-pyridone derivative was obtained in a good yield with 3-trifluoro isomer. On the other hand, unchanged material was recovered completely from the 4-isomer.

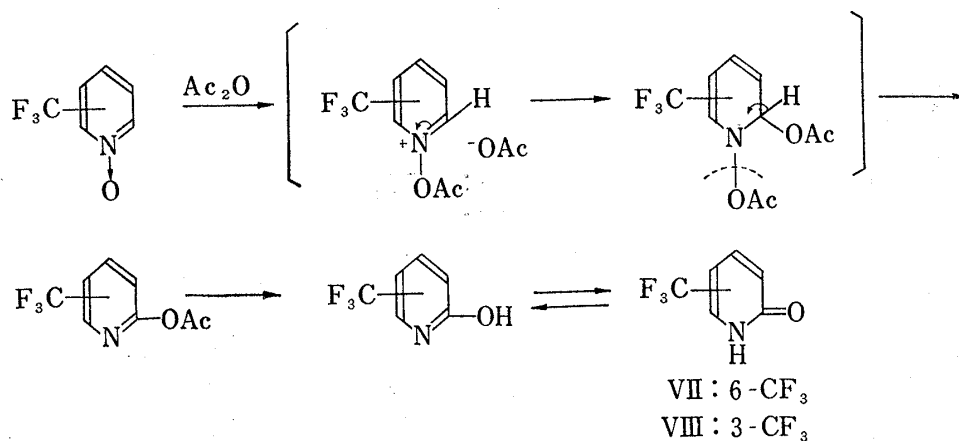


Chart 2

Since this reaction with pyridine 1-oxides in general proceeds in a good yield, the fact that 2- and 4-trifluoromethyl isomers, especially the latter, is resistant against the reaction should be noted. This is presumed to be due to the electronic effect of the trifluoromethyl group. To explain its stronger effect at 4-position than that at 2-position, I effect is not sufficient; we must conclude that, owing to the greater stability of *p*-quinoid than *o*-quinoid in the hyperconjugation⁷⁾ shown in Chart 3, the decrease of minus charge on the oxygen atom is greater in 4-trifluoromethyl than in 2-trifluoromethyl isomer, whereby the former prevents addition of acetyl cation more strongly. With 3-trifluoromethyl isomer,

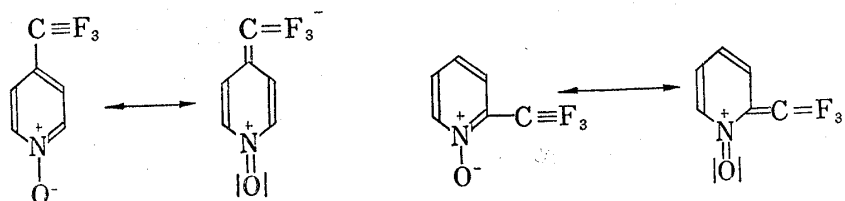


Chart 3

5) M. Katada, *Yakugaku Zasshi*, **67**, 51 (1947).

6) Numbering is done giving precedence to trifluoromethyl group in this case.

7) J.D. Roberts, R.L. Webb, and E.A. McElhill, *J. Am. Chem. Soc.*, **72**, 408 (1950).

in its turn, the phenomenon can be explained as follows: The lone pair electrons on the oxygen atom of N→O group and the trifluoromethyl group are not conjugated, the attack of the electrophilic reagent on 2-position was promoted, and 2-pyridone derivative was formed in a good yield as evidenced by the result of mass spectrometry.^{4b)}

The structures of the products, 6- and 3-trifluoromethyl-2(1H)-pyridone (VII and VIII), were supported by the C=O stretching absorption bands specific to pyridones in their IR spectra and from the results of NMR analysis shown in Table I.

As has been discussed, since the effect of the trifluoromethyl group was very conspicuous in the reaction with acetic anhydride, we next examined the reaction with benzoyl chloride and potassium cyanide.⁸⁾ The reaction is an application of the Reissert reaction to N-oxides; although the reactions proceed smoothly with general quinoline 1-oxides, no successful attempt has been reported with the pyridine series except with 4-chloropyridine 1-oxide.^{8b)}

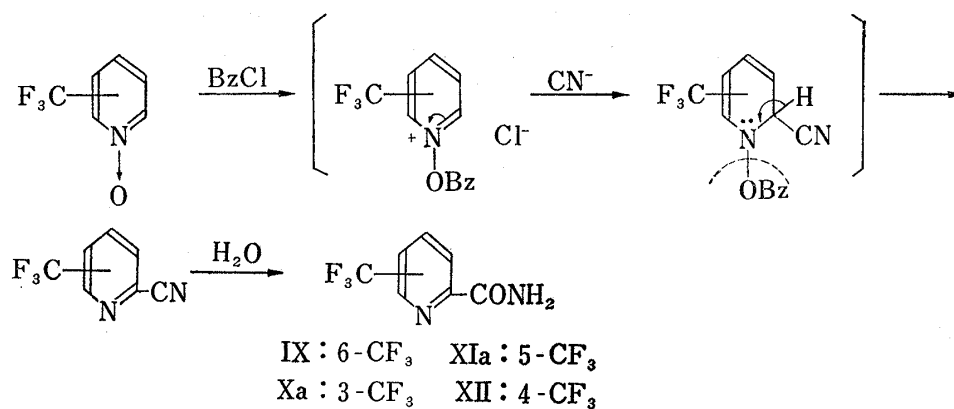


Chart 4

First, 2-trifluoromethylpyridine 1-oxide was derived to its amide with sodium carbonate and hydrogen peroxide to make the isolation easy after the reaction, and 6-trifluoromethylpicolinamide (IX) was obtained in 63% yield. The same reaction with 3-trifluoromethylpyridine 1-oxide gave, by separation with alumina chromatography, 3-trifluoromethylpicolinonitrile (X) and 5-trifluoromethylpicolinonitrile (XI) as oils, whose structures were assumed from their NMR, and 5-trifluoromethylpicolinamide (XIa) as crystals. X and XI were hydrolysed by the above-mentioned method, and their respective amides, Xa and XIa, were obtained in 17% and 48% yields.

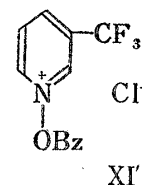


Chart 5

The reason why the 6-amide derivative was greater in amount than 2-amide derivative must be that, 2-position being placed between the electronegative trifluoromethyl group and benzoyloxy group in the intermediate (XI'), 6-position was attacked by cyano anion in preference to 2-position; taking into consideration the reaction with acetic anhydride, we think that the steric bulkiness of benzoyl and acetyl contributes to the reaction. In chromatography, 2-cyano derivative was eluted without being changed but 6-cyano derivative was mostly hydrolysed; therefore, it is presumed that 2-cyano group was protected from hydrolysis by 3-trifluoromethyl group, whereas 6-cyano group had no such protection.

4-Trifluoromethylpyridine 1-oxide was treated in the same manner as 2-trifluoromethyl isomer, and 4-trifluoromethylpicolinamide (XII) was obtained in a good yield of 72%. The structure of the products was determined by elemental analysis and NMR shown in Table I. The point to be noted is that C₅-H appeared in a lower field than C₄-H in IX, which is due to the anisotropic effect of the amide group; with XII, C₃-H shifted to a lower field in the same

8) a) M. Henze, *Chem. Ber.*, **69**, 1566 (1936); b) E. Ochiai and I. Nakayama, *Yakugaku Zasshi*, **65**, 582 (1945).

degree. We could not compare Xa and XIa on that point owing to their being sparingly soluble in deuterio-chloroform, acetone, and so on.

To sum up the above discussion, on pyridine N-oxides possessing trifluoromethyl group, contrary to the general pyridine N-oxides, the effect of trifluoromethyl group was remarkable in that the Reissert reaction proceeded smoothly; but, when the result of the reaction with acetic anhydride was taken into consideration, we deduce that, because of the greater affinity of benzoyl chloride to N-oxides than that of acetic anhydride, the former overcame the effect of trifluoromethyl group to prevent the adduct formation, but once an adduct was formed, the nucleophilic attack of cyano anion was promoted by the electron-withdrawing effect of trifluoromethyl group.

TABLE I. Chemical Shifts^{a)} and Coupling Constants^{b)} of Nucleus Protons of Trifluoromethylpyridine Derivatives

		Position of CF ₃	Position of proton					<i>J</i> ₂₋₃	<i>J</i> ₃₋₄	<i>J</i> ₄₋₅	<i>J</i> ₅₋₆
			2	3	4	5	6				
N-oxide	(I)	2	—	(7.4	~	7.8)	8.44	—	unanalyzable		6.0
	(II)	3	8.00	—	6.9	6.85	7.89	—	—	rather broad	
	(III)	4	8.29	7.53	—	7.53	8.29	6.2	—	—	6.2
Pyridinone	(VII)	6	—	7.00	7.75	7.06	—	—	7.5	7.5	—
	(VIII)	3	—	—	7.71	6.40	7.87	—	—	7.0	7.0
Nitrile (or amide)	(IX)	2	—	7.84	8.09	8.43	—	—	7.5	7.5	—
	(X)	3	—	—	8.21	7.76	9.16	—	—	7.5	5.0
	(XI)	3	8.99	—	8.16	7.89	—	—	—	7.5	—
	(XII)	4	—	8.56	—	7.76	8.87	—	—	—	6.0

a) δ (ppm) from TMS

b) *J*: cps

Experimental

2-Trifluoromethylpyridine 1-Oxide (I)—To a solution of 2-trifluoromethylpyridine (5.0 g) in AcOH (20 ml), 30% H₂O₂ (8 ml) was added and the mixture was heated at about 90° on a water bath for 3 hr; then 5 ml of H₂O₂ was added further, heating being continued for 15 hr. After adding water to the reaction mixture, it was concentrated *in vacuo*, and the procedure was repeated several times. The residue was neutralized with solid Na₂CO₃ and extracted with CHCl₃. After being dried over Na₂SO₄, the extract gave the N-oxide (I) by distillation. bp 132–133° (20 mmHg); yield, 4.5 g (81.3%). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ : 270.8, $\lambda_{\text{max}}^{\text{dioxan}}$ m μ : 279.0. IR cm⁻¹: $\nu_{\text{N-O}}$ 1265 (film). Anal. Calcd. for C₆H₄ONF₃: C, 44.18; H, 2.47; N, 8.58; F, 34.95. Found: C, 44.18; H, 2.59; N, 8.53; F, 35.40.

3-Trifluoromethylpyridine 1-Oxide (II)—To a solution of 3-trifluoromethylpyridine (0.5 g) in AcOH (5.6 ml), 30% H₂O₂ (1 ml) was added and the mixture was heated at about 90° on a water bath for 9 hr; then further 1 ml of H₂O₂ was added, heating being continued for 15 hr. The reaction mixture was worked up as in the case of I, and the N-oxide (0.4 g, 72%) was obtained by distillation at 100–110°/1.5 mmHg (bath temp.); mp 75–77°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 271.5 (4.08), $\lambda_{\text{max}}^{\text{dioxan}}$ m μ (log ϵ): 283.6 (4.11). IR cm⁻¹: $\nu_{\text{N-O}}$ 1256 (KBr). Anal. Calcd. for C₆H₄ONF₃: C, 44.18; H, 2.47; N, 8.58; F, 34.95. Found: C, 44.07; H, 2.58; N, 8.21; F, 34.21.

4-Trifluoromethylpyridine 1-Oxide (III)—To a solution of 4-trifluoromethylpyridine (1.1 g) in AcOH (10 ml), 30% H₂O₂ (2.5 ml) was added and the mixture was heated at about 90° on a water bath for 10 hr; then further 2 ml of H₂O₂ was added, heating being continued for 12 hr. The reaction mixture was worked up as for I. After CHCl₃ was distilled off, the N-oxide remained as crystals. Recrystallization from acetone gave colorless prisms, mp 175–177°; yield, 0.95 g (77%). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 276.5 (4.14), $\lambda_{\text{max}}^{\text{dioxan}}$ m μ (log ϵ): 287.0 (4.18). IR cm⁻¹: $\nu_{\text{N-O}}$ 1265 (KBr). Anal. Calcd. for C₆H₄ONF₃: C, 44.18; H, 2.49; N, 8.58; F, 34.95. Found: C, 44.02; H, 2.47; N, 8.40; F, 34.51.

2,5-Bis(trifluoromethyl)pyridine 1-Oxide (IV)—To a solution of 2,5-bis(trifluoromethyl)pyridine (1.0 g) in AcOH (6 ml), 30% H₂O₂ (2 ml) was added and the mixture was heated at 90° on a water bath for 24 hr. The reaction mixture was worked up as for I. After CHCl₃ was evaporated, the residue was recrystallized from a mixture of benzene and hexane to colorless prisms, mp 90–91°; yield, 0.1 g (9%). IR cm⁻¹: $\nu_{\text{N-O}}$ 1258 (KBr). Anal. Calcd. for C₇H₃ONF₆: C, 36.37; H, 1.31; N, 6.06; F, 49.33. Found: C, 36.18; H, 1.32; N, 6.12; F, 47.66.

2,4-Bis(trifluoromethyl)pyridine 1-Oxide (V)—To a solution of 2,4-bis(trifluoromethyl)pyridine (0.6 g) in CF_3COOH (5 ml), 30% H_2O_2 (2 ml) was added, and the mixture was heated at 80° on a water bath for 20 hr. The reaction mixture was worked up as for I. After CHCl_3 was evaporated, the residue was distilled and a colorless oil (bp $140^\circ/20$ mmHg) was obtained; yield, 0.4 g (62%). IR cm^{-1} : $\nu_{\text{N-O}}$ 1250 (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_3\text{ONF}_6$: C, 36.37; H, 1.31; N, 6.06; F, 49.33. Found: C, 36.18; H, 1.40; N, 6.20; F, 47.19.

2,6-Bis(trifluoromethyl)pyridine 1-Oxide (VI)—To a solution of 2,6-bis(trifluoromethyl)pyridine (3.0 g) in CF_3COOH (20 ml), 30% H_2O_2 (6 ml) was added, and the mixture was heated at 80° on a water bath for 7 hr; then 2 ml of H_2O_2 was added and heated further for 12 hr. CF_3COOH and the starting material were distilled off *in vacuo*, the residue was made alkaline with Na_2CO_3 , and it was extracted with CHCl_3 . After being dried over Na_2SO_4 , CHCl_3 was evaporated, and the residue was recrystallized from a mixture of benzene and petr. ether to colorless sands, mp 100° ; yield, 0.9 g (27%). IR cm^{-1} : $\nu_{\text{N-O}}$ 1269 (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_3\text{ONF}_6$: C, 36.37; H, 1.31; N, 6.06; F, 49.33. Found: C, 36.38; H, 1.40; N, 6.27; F, 49.33.

6-Trifluoromethyl-2(1H)-pyridinone (VII)—A solution of I (0.9 g) in Ac_2O (4 ml) was refluxed for 12 hr. The reaction mixture was concentrated *in vacuo*; the residue was dissolved in H_2O , made alkaline with NaHCO_3 , and extracted with CHCl_3 . The extract was dried over Na_2SO_4 and the solvent evaporated. The residue was dissolved in MeOH (10 ml), added with conc. HCl (1 ml), and refluxed for 1 hr. After removing MeOH, the residue was made alkaline with NaHCO_3 and extracted with CHCl_3 . CHCl_3 was evaporated, the residue was treated with dil. AcOH, and the precipitate was collected by filtration. Recrystallization of this residue from benzene gave VII as colorless needles, mp $120\text{--}121^\circ$; yield, 0.2 g (22%). *Anal.* Calcd. for $\text{C}_6\text{H}_4\text{ONF}_3$: C, 44.18; H, 2.47; N, 8.58; F, 34.95. Found: C, 44.27; H, 2.57; N, 8.40; F, 35.47.

Unchanged material (0.3 g) was recovered from dil. AcOH by making it alkaline and extracting with CHCl_3 .

3-Trifluoromethyl-2(1H)-pyridinone (VIII)—A solution of II (0.3 g) in Ac_2O (3 ml) was refluxed for 10 hr. The reaction mixture was evaporated to dryness *in vacuo*, basified, and extracted with CHCl_3 . The solvent was removed from the extract and the residue was recrystallized from benzene-hexane to colorless needles (VIII), mp $153\text{--}153.5^\circ$; yield, 0.25 g (83%). IR cm^{-1} : $\nu_{\text{C=O}}$ 1676 (KBr). *Anal.* Calcd. for $\text{C}_6\text{H}_4\text{ONF}_3$: C, 44.18; H, 2.47; N, 8.58; F, 34.95. Found: C, 44.19; H, 2.55; N, 8.23; F, 34.55.

Reaction of 4-Trifluoromethylpyridine 1-Oxide (III) with Ac_2O —A solution of III (0.3 g) in Ac_2O (5 ml) was refluxed for 20 hr. The reaction mixture was worked up as above and the unchanged material (0.28 g) was recovered.

6-Trifluoromethylpicolinamide (IX)—To a mixture of the solution of I (0.7 g) in CHCl_3 (3 ml) and the solution of KCN (0.5 g) in H_2O (5 ml), a solution of BzCl (0.8 g) in CHCl_3 (10 ml) was added dropwise with stirring and ice-cooling. After 3 hr of stirring the reaction mixture was extracted with CHCl_3 , which was dried over Na_2SO_4 , concentrated *in vacuo*, and purified by Al_2O_3 chromatography with CHCl_3 .

The solvent was evaporated from the elution and 10% Na_2CO_3 (10 ml), 3% H_2O_2 (10 ml), and $(\text{CH}_3)_2\text{CO}$ (5 ml) were added to the residue, which was allowed to stand overnight. The reaction mixture was extracted with CHCl_3 , the extract was dried over Na_2SO_4 , and the solvent was evaporated. The residue was recrystallized to 0.5 g (63%) of IX as colorless needles, mp 110° . IR cm^{-1} : $\nu_{\text{C=O}}$ 1660 (broad) (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_5\text{ON}_2\text{F}_3$: C, 44.22; H, 2.65; N, 14.74; F, 29.98. Found: C, 44.33; H, 2.69; N, 14.68; F, 29.89.

Reaction of 3-Trifluoromethylpyridine 1-Oxide (II) with BzCl-KCN —To the mixture of a solution of II (0.5 g) in CHCl_3 (10 ml) and a solution of KCN (0.5 g) in H_2O (4 ml), a solution of BzCl (0.6 g) in CHCl_3 (10 ml) was added dropwise with stirring and ice-cooling. After 6 hr of stirring, the reaction mixture was extracted with CHCl_3 and, after working up as above, the extract was purified by Al_2O_3 chromatography. 5-Trifluoromethylpicolinonitrile (XI) (IR cm^{-1} : $\nu_{\text{C}\equiv\text{N}}$ 2260 (CCl_4)) and 3-trifluoromethylpicolinonitrile (X) (IR cm^{-1} : $\nu_{\text{C}\equiv\text{N}}$ 2270 (CCl_4)) were eluted as oils in this order.

XIa was eluted with CHCl_3 . Xa and XIa were obtained from X and XI, respectively, by hydrolysis with $\text{Na}_2\text{CO}_3\text{--H}_2\text{O}_2$ as for IX. Xa was recrystallized from benzene and 0.1 g (17%) of colorless sands, mp $129\text{--}130^\circ$, was obtained. IR cm^{-1} : $\nu_{\text{C=O}}$ 1718 (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_5\text{ON}_2\text{F}_3$ (3-trifluoromethylpicolinamide): C, 44.22; H, 2.65; N, 14.74; F, 29.98. Found: C, 44.22; H, 2.71; N, 14.85; F, 29.90.

XIa was recrystallized from benzene and 0.2 g (48%) of feathers, mp $169\text{--}170^\circ$, was obtained. IR cm^{-1} : $\nu_{\text{C=O}}$ 1711 (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_5\text{ON}_2\text{F}_3$ (5-trifluoromethylpicolinamide); C, 44.22; H, 2.65; N, 14.74; F, 29.98. Found: C, 44.43; H, 2.78; N, 14.79; F, 29.58.

4-Trifluoromethylpicolinamide (XII)—To the mixture of a solution of III (0.3 g) in CHCl_3 (10 ml) and a solution of KCN (0.3 g) in H_2O (5 ml), a solution of BzCl (0.3 g) in CHCl_3 (10 ml) was added dropwise with stirring and ice-cooling. After 7 hr of stirring, the reaction mixture was worked up and purified as above. Recrystallization from benzene gave 0.25 g of colorless needles, mp $128\text{--}129^\circ$. IR cm^{-1} : $\nu_{\text{C=O}}$ 1690 (KBr). *Anal.* Calcd. for $\text{C}_7\text{H}_5\text{ON}_2\text{F}_3$: C, 44.22; H, 2.65; N, 14.74. Found: C, 43.79; H, 2.62; N, 14.93.

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