[Chem. Pharm. Bull.
17(11)2335—2339(1969)]

UDC 547.831.4.04

Studies on Organic Fluorine Compounds. VI.[1] Preparations and Reactions of (Trifluoromethyl)quinoline N-Oxides

Yoshiro Kobayashi, Itsumaro Kumadaki,
and Shigeru Taguchi

Tokyo College of Pharmacy[2]

(Received June 24, 1969)

First, 2-, 3-, and 4-(trifluoromethyl)quinoline 1-oxides (IV, V, and VI) were synthesized. Next, their reactions with acetic anhydride and phosphoryl chloride and the Reissert reaction were carried out and compared with the reactions in the cases of pyridine series. The reactions of IV with acetic anhydride and phosphoryl chloride gave 4-substituted products, whereas in the cases of V and VI 2-substituted products were obtained. In the Reissert reaction of IV, the starting material was recovered; in the cases of V and VI, 2-nitrile derivative was produced as well as a considerable amount of 2-hydroxy derivative as by-product. Then, the reaction of V with only potassium cyanide in methanol was carried out to obtain 3-(trifluoromethyl)cinchoninonitrile. The unique result as above was concluded to be due to the naphthoid structure of quinoline.

In the previous paper,[1] on examining the reactions of (trifluoromethyl)pyridine N-oxides, we elucidated the effect the trifluoromethyl group has on the reactivity of the pyridine ring. The most notable fact concerning it is that the trifluoromethyl group possesses not only an electron withdrawing effect but also a hyperconjugation effect (Chart 1).

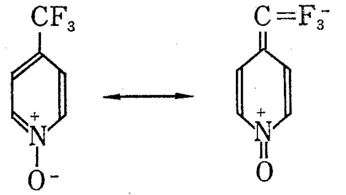


Chart 1

As regards (trifluoromethyl)quinolines, those possessing trifluoromethyl groups in the benzene part of quinolines had been synthesized by the Skraup reaction using the corresponding aminobenzotrifluorides,[3] and a few reports have been published concerning their utilization in the fields of analytical reagents[4] and drugs.[5] As for those with trifluoromethyl groups in the pyridine part of quinolines, 2-(trifluoromethyl)quinoline was recently synthesized by the reaction of quinaldic acid with sulfur tetrafluoride,[6] but there is no report on the successful synthesis of 3- or 4-(trifluoromethyl)quinoline. In this paper, we report that 2-, 3-, and 4-(trifluoromethyl)quinolines (I, II, and III) were synthesized and converted to their N-oxides, and that the reactivity of the latter was compared with the N-oxides of (trifluoromethyl)pyridines.

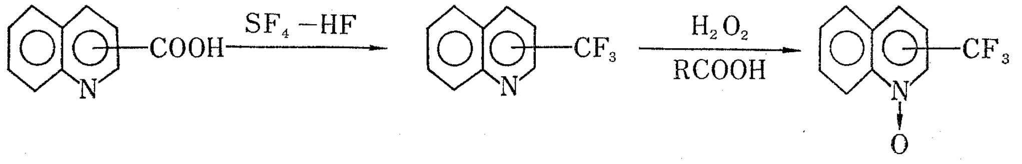
First, 2-, 3-, and 4-(trifluoromethyl)quinolines were prepared by the reactions of the corresponding carboxylic acids with sulfur tetrafluoride in the presence of hydrogen fluoride. In the cases of the latter two products, yields were 42% and 69%, respectively. The structure of each product was determined by elemental analysis and infrared (IR) spectrum.

Next, N-oxidation of each (trifluoromethyl)quinoline was carried out. While mono-(trifluoromethyl)pyridines all gave N-oxides in a good yield by heating them with acetic acid and

---

[1] Part V: Y. Kobayashi and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **17**, 510 (1969).
[2] Location: *Kashiwagi 4-chome, Shinjuku-ku, Tokyo.*
[3] E. Pouterman and A. Girardt, *Helv. Chim. Acta*, **30**, 107 (1947).
[4] R. Belcher, M. Stacey, A. Sykes, and J.C. Tatlow, *J. Chem. Soc.*, **1954**, 3846.
[5] H. Gilman, L. Tolman, F. Yeoman, L.A. Woods, D.A. Shirley, and S. Avakian, *J. Am. Chem. Soc.*, **68**, 426 (1946).
[6] M.S. Raasch, *J. Org. Chem.*, **27**, 1406 (1962).

hydrogen peroxide, and in spite of the fact that 3- and 4-(trifluoromethyl)quinolines gave the corresponding N-oxides (V and VI) under the same reaction conditions, 2-(trifluoromethyl)-quinoline gave N-oxide (IV) only when trifluoroacetic acid and hydrogen peroxide were used. The fact may be due to the stronger electron withdrawing effect of the trifluoromethyl group in 2-(trifluoromethyl)quinoline than those in the pyridine series caused by the naphthoid structure of the former, or to the added steric effect. The structure of these products was determined by elemental analysis, IR spectrum, and the reactions which will be discussed later.



position of	CF_3	R		CF_3	Yield (%)
I	2	CF_3	IV	2	51
II	3	CH_3	V	3	81
III	4	CH_3	VI	4	68

Chart 2

Then, the rearrangement of the N-oxides by acetic anhydride, which remarkably revealed the effect of trifluoromethyl groups in the case of the pyridine series, was carried out. That is, with 2-(trifluoromethyl)pyridine 1-oxide,its rearranged product was hardly given and with 4-(trifluoromethyl)pyridine 1-oxide, only the unchanged material was recovered; while, as for 2-(trifluoromethyl)quinoline 1-oxide (IV), 4-hydroxy derivative (VII) was given, and 3- and 4-(trifluoromethyl)quinoline 1-oxides (V and VI), 1-*H*-2-oxo derivatives (VIII and IX) in good yields. The reasonable explanation of the above fact is that, contrary to the case of pyridine rings, activation of quinoline rings by means of naphthoid structure overcame the effect of trifluoromethyl group to prevent the reaction. Because 2-position was blocked by a trifluoromethyl group, VII was produced from IV, an example similar to which can be seen in the case of 2-phenylquinoline 1-oxide,[7] this is contrary to the fact that ω-hydroxy derivative was produced in the case of quinaldine 1-oxide.[8] Although there is a report[9] that the similar rearrangement of 4-cyanoquinoline 1-oxide gave, besides 2-hydroxy derivative, 3-hydroxy derivative with Michael type addition owing to the activation of C_3–C_4 double bond by CN,

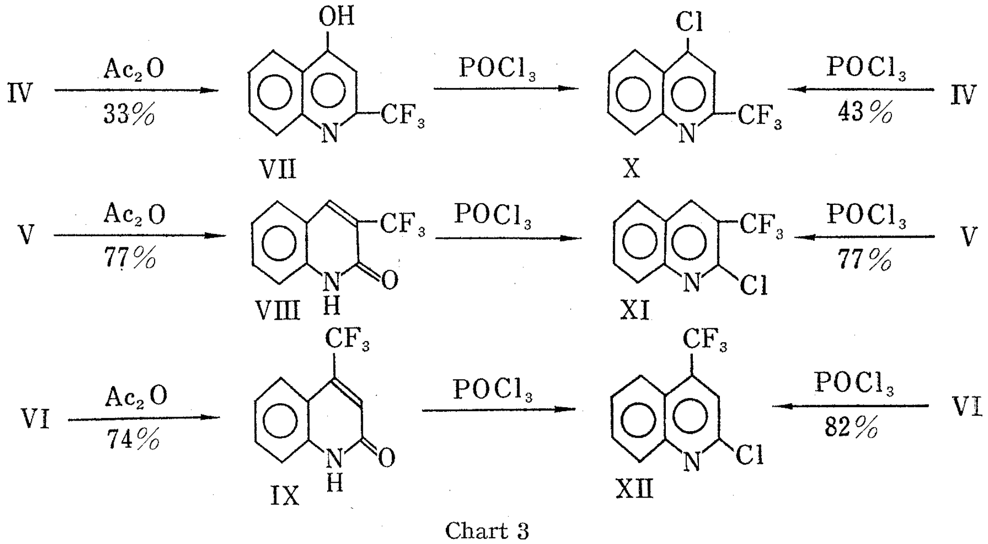


Chart 3

---

[7] M. Hamana and K. Shimizu, *Yakugaku Zasshi*, **86**, 59 (1966).

[8] G. Kobayashi, S. Furukawa, and Y. Akimoto, *Yakugaku Zasshi*, **74**, 791 (1954).

[9] H.U. Daeniker and J. Druey, *Helv. Chim. Acta*, **41**, 2149 (1958).

we could not find it in our product. The result suggests that +M effect of trifluoromethyl group is smaller than that of cyano group.

Next, the reactions of each N-oxide with phosphoryl chloride proceeded in parallel with those in the case of acetic anhydride, and 4-chloro derivative (X) from IV and each corresponding 2-chloro derivative (XI and XII) from V and VI were produced. The structure of X, XI, and XII was determined by elemental analysis and nuclear magnetic resonance (NMR) spectrum. The structure of the rearranged products (VII, VIII, and IX) by acetic anhydride mentioned above was determined by elemental analysis, IR spectrum, and the fact that they were converted to X, XI, and XII, respectively, by boiling them with phosphoryl chloride.

Then, the reaction of N-oxide with benzoyl chloride and potassium cyanide, the so-called Reissert reaction was carried out. Although this reaction dose not proceed in the cases of pyridine N-oxides generally, in the cases of (trifluoromethyl)-pyridine N-oxides, their amide derivatives *via* cyano derivatives were obtained in good yields. This time, in the case of the quinoline series, IV gave the unchanged material because of the blocking at 2-position by a trifluoromethyl group, but V and VI gave 2-hydroxy derivatives (VIII and IX) in fairly good yields beside the expected 2-cyano derivatives (XIII and XIV). The structure of XIII and XIV was determined by elemental analysis and IR and NMR spectrum.

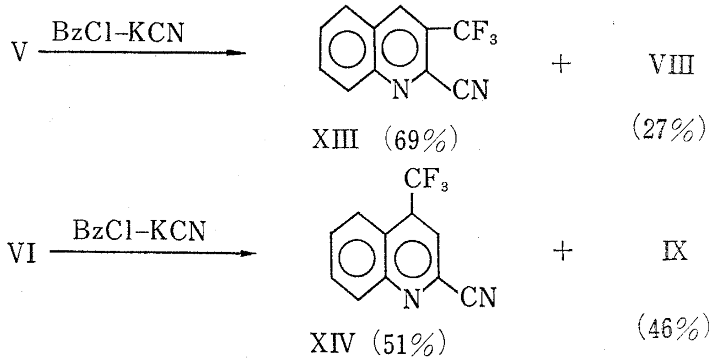


Chart 4

The fact to be noted in the above case is the production of VIII and IX as by-product, which may be logically explained thus: O-benzoyl adducts of V and VI, being activated by the electron withdrawing effect of a trifluoromethyl group, reacted with the solvent water on the instant of their formation and before the attack by cyano anion.

To sum up the above discussion, although its electron withdrawing effect was shown as the effect of trifluoromethyl groups in N-oxidation and the Reissert reaction, the remarkable effect comparable to that in the case of the pyridine series was not observed in the rearrangement by acetic anhydride. The fact may be attributed to the activation by the naphthoid structure of quinoline ring.

In order to make the above two effects occur simultaneously, 3-(trifluoromethyl)quinoline 1-oxide should be treated with nucleophile, so that the hyperconjugation effect observed in the pyridine series could be conducted through the double bonds fixed by the naphthoid structure in quinoline rings, thereby making 4-position more ready to be attacked than 2-position. Therefore, V was treated with potassium cyanide in methanol; and even when the reaction temperature was as low as 30°, 3-(trifluoromethyl)cinchoninonitrile (XV) was obtained in 48% yield. The reaction mechanism was assumed as shown in Chart 5.

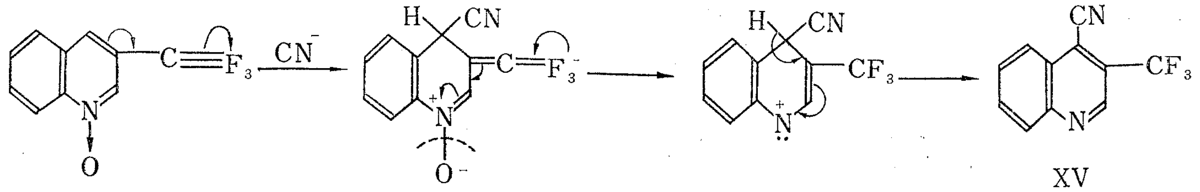


Chart 5

In the case of the quinoline series, because of the strong activation by means of naphthoid structure, the effect of trifluoromethyl group is not so remarkable as in the case of the pyridine series; by the careful selection of the reaction conditions as above, however, completely new types of reactions owing to the activation by means of naphthoid structure could be ascertained to take place. In the above reaction, pale yellow crystals of mp 154—155° were producted as by-product, whose structure is now being examined.

Experimental

3-(Trifluoromethyl)quinoline (II)——In a 50 ml "Hastelloy-C"-lined autoclave with a magnetic stirrer, quinoline-3-carboxylic acid (15 g), anhydrous HF (5 ml), and SF_4 (15 ml) were heated at 170° for 24 hr with stirring. After the reaction mixture was cooled to room temp., gases were discharged and the remaining solution was poured into ice water. When it was made alkaline with 10% NaOH, its steam-distillation was carried out. The distillate was extracted with ether and the extract was dried over Na_2SO_4. After the evaporation of ether, the residue was distilled *in vacuo* to give faint-yellow oil, bp 110° (15 mmHg). Yield, 7 g (42%). IR cm^{-1}: ν_{CF_3} 1305, 1135 (broad) (Nujol). NMR (in $CDCl_3$) τ: 0.90 (1H, doublet, J=2.5 cps, 2-H), 1.58 (1H, doublet, J=2.5 cps, 4-H), 1.82 (1H, doublet, J=7.5 cps, 8-H). *Anal.* Calcd. for $C_{10}H_6NF_3$: C, 60.91; H, 3.07; N, 7.11; F, 28.91. Found: C, 60.54; H, 3.06; N, 7.20; F, 27.29.

4-(Trifluoromethyl)quinoline (III)——Cinchonic acid (10 g), HF (5 ml), and SF_4 (13 ml) were heated at 150° for 17 hr in the same manner as above. After the reaction mixture was worked up as above, faintly yellow oil, bp 139° (25 mmHg), was obtained. Yield, 7.8 g (69%). IR cm^{-1}: ν_{CF_3} 1328, 1140 (KBr). NMR (in $CDCl_3$) τ: 0.99 (1H, doublet, J=5 cps, 2-H).

Picrate (from MeOH); yellow needles, mp 160—162°. *Anal.* Calcd. for $C_{16}H_9O_7N_4F_3$: C, 45.08; H, 2.13; N, 13.14; F, 13.37. Found: C, 45.27; H, 2.31; N, 13.58; F, 12.95.

2-(Trifluoromethyl)quinoline 1-Oxide (IV)——To a solution of 2-(trifluoromethyl)quinoline (5.5 g) in CF_3COOH (30 ml), 30% H_2O_2 (5 ml) was added, and the mixture was refluxed gently on a water bath for 3 hr; then 5 ml of H_2O_2 was added and it was heated further for 17 hr. The reaction mixture was concentrated to the half volume *in vacuo*, and after the addition of water it was concentrated again; the procedure was repeated three times. The residue was basified with Na_2CO_3 and extracted with CH_2Cl_2. After being dried over Na_2SO_4, the solvent was evaporated and the residue was recrystallized from CCl_4 to pale-yellow sands, mp 100—101°. Yield, 3.0 g (51%). IR cm^{-1}: ν_{CF_3} 1330, 1150 (broad), ν_{N-O} 1245 (KBr). NMR shows no 2-H signal. *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58; F, 26.73. Found: C, 56.32; H, 2.96; N, 6.89; F, 27.03.

3-(Trifluoromethyl)quinoline 1-Oxide (V)——To a solution of II (5.5 g) in AcOH (10 ml), 30% H_2O_2 (3 ml) was added, and the mixture was heated at 70—80° on a water bath for 3 hr; then 30% H_2O_2 was added and it was heated further for 17 hr. The reaction mixture was worked up as in the case of IV to afford faintly yellow needles, mp 116—118°. Yield, 4.8 g (81%). IR cm^{-1}: ν_{CF_3} 1380, 1132; ν_{N-O} 1228 (KBr). *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58; F, 26.73. Found: C, 56.13; H, 2.84; N, 6.90; F, 27.36.

4-(Trifluoromethyl)quinoline 1-Oxide (VI)——III (5.4 g) was treated in the same manner as in the case of V, and yellow plates, mp 116—118°, was obtained. Yield, 4.0 g (68.5%). IR cm^{-1}: ν_{CF_3} 1323, 1123, ν_{N-O} 1242 (KBr). *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58. Found: C, 56.05; H, 2.94; N, 6.42.

2-(Trifluoromethyl)-4-quinolinol (VII)——A solution of IV (0.3 g) in Ac_2O (8 ml) was refluxed for 10 hr. After Ac_2O was distilled off *in vacuo*, 10% HCl (0.2 ml) and EtOH (5 ml) were added to the residue; the solution was concentrated *in vacuo*, basified with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, concentrated, and chromatographed over Al_2O_3. Elution with CH_2Cl_2 gave the starting material I (0.02 g), and elution with MeOH–CH_2Cl_2 (1:4) gave colorless needles (recrystallized from MeOH), mp 202—205°. Yield, 0.1 g (33%). IR cm^{-1}: ν_{N-H} 3300—2000, ν_{CF_3} 1322, 1145 (broad) (KBr). *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58; F, 26.72. Found: C, 56.26; H, 2.90; N, 7.08; F, 27.59.

3-(Trifluoromethyl)carbostyril (VIII)——A solution of V (0.3 g) in Ac_2O (8 ml) was refluxed for 10 hr, and the solution was treated as in the case of VII and chromatographed over Al_2O_3. Elution with CH_2Cl_2–MeOH (4:1) gave colorless needles (recrystallized from MeOH), mp 200—203°. Yield, 0.23 g (77%). IR cm^{-1}: ν_{N-H} 3240—2000, $\nu_{C=O}$ 1683 (broad), ν_{CF_3} 1330, 1125 (broad) (KBr). *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58; F, 26.72. Found: C, 56.28; H, 3.06; N, 6.86; F, 26.94.

4-(Trifluoromethyl)carbostyril (IX)——A solution of VI (0.5 g) in Ac_2O (10 ml) was refluxed for 10 hr, and the solution was treated as in the case of VII and chromatographed over Al_2O_3. Elution with $CHCl_3$–CCl_4 (1:1) gave the starting material (0.05 g) and elution with MeOH gave colorless needles, mp 245—246° (recrystallized from MeOH). Yield, 0.37 g (74%). IR cm^{-1}: ν_{N-H} 3200—2000, $\nu_{C=O}$ 1672, ν_{CF_3} 1290, 1134 (KBr). *Anal.* Calcd. for $C_{10}H_6ONF_3$: C, 56.33; H, 2.84; N, 6.58; F, 26.72. Found: C, 56.62; H, 3.06; N, 6.56; F, 25.72.

4-Chloro-2-(trifluoromethyl)quinoline (X)——a) A solution of IV (0.3 g) in $POCl_3$ (3 ml) was refluxed for 3 hr, and after $POCl_3$ was distilled off *in vacuo* the residue was treated with ice water, basified with $NaHCO_3$, and extracted with CH_2Cl_2. After it was dried over Na_2SO_4, CH_2Cl_2 was distilled off and the residue was chromatographed over Al_2O_3. Its elution with C_6H_6 and sublimation *in vacuo* gave colorless prisms, mp 38—39°. Yield, 0.14 g (43.2%). Beilstein test: positive. IR cm^{-1}: ν_{CF_3} 1347, 1143 (broad) (film). NMR (in $CDCl_3$) τ: 2.20 (3-H, singlet), no 2-H absorption. *Anal.* Calcd. for $C_{10}H_5NClF_3$: C, 51.86; H, 2.17; N, 6.05; F, 24.61. Found: C, 51.92; H, 2.33; N, 6.15; F, 24.66.

b) A solution of VII (0.1 g) in $POCl_3$ (1 ml) was refluxed for 3 hr, and the mixture was treated with ice water, basified with $NaHCO_3$, and extracted with $CHCl_3$. After being dried over Na_2SO_4, the solution was concentrated to give faintly yellow oil (0.09 g); and by sublimation *in vacuo* colorless needles, mp 38—39°, were also given. The crystals were identified with X by the mixture melting point and comparing IR spectra.

2-Chloro-3-(trifluoromethyl)quinoline (XI)——a) A solution of V (0.3 g) in $POCl_3$ (3 ml) was treated in the same manner as above; recrystallization of the extract from *n*-hexane gave colorless sands, mp 98—100°. Yield, 0.25 g (77%). Beilstein test: positive. IR cm^{-1}: ν_{CF_3} 1326, 1140 (broad) (KBr). NMR shows no 2-H absorption. *Anal.* Calcd. for $C_{10}H_5NClF_3$: C, 51.86; H, 2.17; N, 6.05; F, 24.61. Found: C, 51.90; H, 2.11; N, 6.11; F, 24.36.

b) A solution of VIII (0.1 g) in $POCl_3$ (2 ml) was refluxed for 1 hr; after the excess $POCl_3$ was distilled off *in vacuo*, the residue was treated with ice water, basified with Na_2CO_3, and extracted with CH_2Cl_2. After it was dried over Na_2SO_4, CH_2Cl_2 was distilled off and the residue was recrystallized from pet. ether to give colorless sands (0.11 g, theoretically). It was identified with XI by the mixture melting point and comparing IR spectra.

2-Chloro-4-(trifluoromethyl)quinoline (XII)——a) A solution of VI (0.3 g) in $POCl_3$ (3 ml) was refluxed for 3 hr; after it was concentrated *in vacuo*, it was treated in the same manner as in the case of X and chromatographed over Al_2O_3. Sublimation of *n*-hexane elute gave colorless prisms, mp 41—42°. Yield, 0.27 g (82%). IR cm^{-1}: ν_{CF_3} 1323, 1123 (broad), ν_{N-O} 1242 (KBr). NMR shows no 2-H signal. *Anal.* Calcd. for $C_{10}H_5NClF_3$: C, 51.86; H, 2.17; N, 6.05; F, 24.61. Found: C, 51.92; H, 2.37; N, 6.06; F, 23.23.

b) A solution of IX (0.2 g) in $POCl_3$ (3 ml) was treated in the same manner as above to give colorless prisms (0.2 g, 92%), which was identified with XII by comparing IR spectra.

3-(Trifluoromethyl)quinaldonitrile (XIII)——To a solution of V (0.18 g) in $CHCl_3$ (2 ml), a solution of KCN (0.3 g) in H_2O (5 ml) was added. Under ice-cooling and stirring, a solution of BzCl (0.3 g) in $CHCl_3$ (3 ml) was added dropwise to the mixture. While stirring was continued for 5 hr, it was warmed to room temp.; it was stirred with 7% solution of $NaHCO_3$ (10 ml) for 1 hr and extracted with $CHCl_3$. After it was dried over Na_2SO_4, $CHCl_3$ was distilled off. The residue was dissolved in CCl_4 and chromatographed over Al_2O_3. The CCl_4 elute was recrystallized from pet. ether to give colorless sands, mp 154—155°. Yield, 0.13 g (69.2%). IR cm^{-1}: $\nu_{C\equiv N}$ 2260, ν_{CF_3} 1375, 1130 (KBr). NMR shows no 2-H signal. *Anal.* Calcd. for $C_{11}H_5N_2F_3$: C, 59.46; H, 2.27; N, 12.61; F, 25.66. Found: C, 59.63; H, 2.31; N, 12.45; F, 25.99.

Elution with $CHCl_3$–MeOH (100:1) gave colorless needles (recrystallized from C_6H_6), mp 203—205°. Yield, 0.05 g (27%). The crystals were identified with VIII by the mixture melting point and comparing IR spectra.

4-(Trifluoromethyl)quinaldonitrile (XIV)——To a solution of VI (0.3 g) in $CHCl_3$ (5 ml), a solution of KCN (0.25 g) in H_2O (5 ml) was added. Under ice-cooling and stirring, a solution of BzCl (0.3 g) in $CHCl_3$ (10 ml) was added dropwise to the mixture. During a 5 hr stirring, it was warmed to room temp.; it was stirred with 7% solution of $NaHCO_3$ (5 ml) for 0.5 hr, and extracted with $CHCl_3$. After it was dried over Na_2SO_4, $CHCl_3$ was distilled off. Addition of CCl_4 gave a precipitate, which was filtered. The filtrate was chromatographed over Al_2O_3 and CCl_4 was evaporated to give white cubes (0.2 g). Recrystallization from iso-Pr_2O–pet. ether gave white prisms, mp 103—104°. Yield, 0.16 g (51%). IR cm^{-1}: $\nu_{C\equiv N}$ 2050 (weak), ν_{CF_3} 1355, 1150 (KBr). NMR shows no 2-H signal. *Anal.* Calcd. for $C_{11}H_5N_2F_3$: C, 59.46; H, 2.27; N, 12.61; F, 25.66. Found: C, 59.68; H, 2.11; N, 12.91; F, 23.83.

A $CHCl_3$–EtOH (20:1) elute and the precipitate mentioned above were recrystallized from MeOH to give white prisms, mp 245—246°. Yield, 0.14 g (46%). The crystals were identified with IX by the mixture melting point and comparing IR spectra.

The same reaction with IV only gave the starting material.

3-(Trifluoromethyl)cinchoninonitrile (XV)——To a solution of V (0.5 g) in MeOH (20 ml), KCN (0.3 g) was added and the mixture was kept at 30° for 8.5 hr till it gradually turned to dark purple. MeOH was distilled off *in vacuo*, and it was extracted with CH_2Cl_2 after the addition of water and dried over Na_2SO_4. After CH_2Cl_2 was distilled off, it was chromatographed over Al_2O_3. The hexane elute was recrystallized from MeOH to give colorless prisms, mp 104—104.5°. Yield, 0.25 g (48%). IR cm^{-1}: $\nu_{C\equiv N}$ 2270, ν_{CF_3} 1340, 1142 (broad) (KBr). NMR τ: 0.76 (1H, singlet, 2-H). *Anal.* Calcd. for $C_{11}H_5N_2F_3$: C, 59.46; H, 2.27; N, 12.61; F, 25.66. Found: C, 60.07; H, 2.07; N, 13.03; F, 23.57. M.W. Calcd. for $C_{11}H_5N_2F_3$: 222. Found (by mass spectrometry): 222.

Recrystallization of C_6H_6–*n*-hexane elute (1:4) gave pale yellow cubes, mp 154—155° (recrystallized from MeOH). Yield, 0.16 g.

Acknowledgement We express our sincere gratitude to Hoansha, whose grant enabled us to carry out a part of the above experiment, to Sankyo Co. for elemental analyses, and to Mr. T. Ono for the measurement of NMR spectra.