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Studies on Organic Fluorine Compounds. VIII.[1] Alcoholysis of (Trifluoromethyl)quinolines[2]

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In the studies of alcoholyses of (trifluoromethyl) quinolines, 3-(trifluoromethyl) compounds (II and V) were found to be more reactive to nucleophile than other isomers (I, III, IV, and VI), which were more reactive than benzotrifluoride, in turn. Two different mechanisms are proposed for each process. Reduction of N-oxide groups with sodium alkoxides are also reported.

The trifluoromethyl group has been referred as a very stable group, whose reaction, except its hydrolysis in 100% sulfuric acid, has never been reported to date.[4] On the other hand, we reported the effect of this group on the reactivities of pyridine and quinoline derivatives.[5] In this paper, we report the effect of the nitrogen atom in a heterocycle on the nucleophilic substitution reaction at the carbon atom of a trifluoromethyl group.

As regards the nucleophilic attack on (trifluoromethyl) quinolines, three types of reaction, according to the position of trifluoromethyl group, are expected as shown in Chart 1.

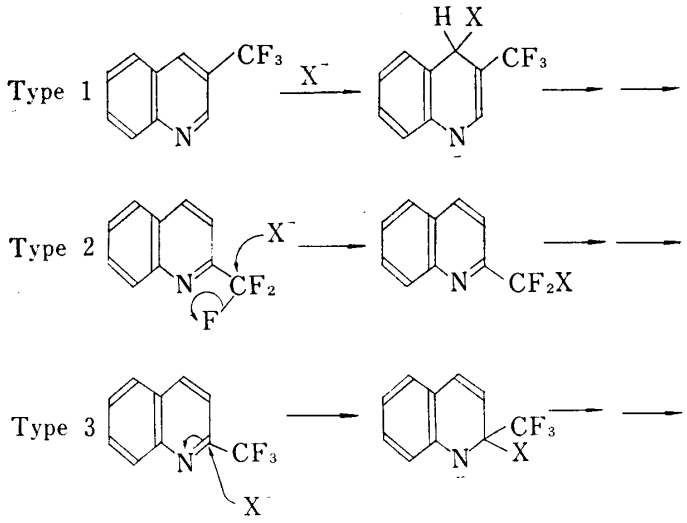

Chart 1

Type 1 is expected in the case of 3-(trifluoromethyl) quinoline; the electronic effect of trifluoromethyl group and of the nitrogen atom in the ring makes 4-position susceptible to nucleophilic attack. An example of this type is known in the reaction of 3-(trifluoromethyl) quinoline 1-oxide with potassium cyanide.[5b] Type 2 is an S_N2 reaction; the nucleophile attacks the carbon atom of trifluoromethyl group, which seems to be more electrophilic than that of benzotrifluoride owing to the effect of the nitrogen atom in the ring. Type 3 is an S_NAr reaction involving Meisenheimer-type complex; this is expected from the fact that the trifluoromethyl group is often referred as a pseudohalogen,[6] but no examples of such a reaction with carbon–carbon bond fission are known, except for the

1) Part VII: Y. Kobayashi, I. Kumadaki, S. Sato, N. Hara, and E. Chikami, *Chem. Pharm. Bull.* (Tokyo), **18**, 2334 (1970).
2) Presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: Kitashinjuku 3-*chome*, *Shinjuku-ku*, *Tokyo*.
4) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, 1969, p. 410.
5) *a*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **17**, 510 (1969); *b*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **17**, 2335 (1969).
6) Ref.[4] p. 62.

haloform reaction. From the above consideration, type 1 reaction is expected to take place with 3-(trifluoromethyl) quinoline, and types 2 and 3 with 2-and 4-(trifluoromethyl) quinolines.

On the other hand, from the consideration of mass spectrum of (trifluoromethyl) pyridines, we reported[7] that α-trifluoromethyl group on the pyridine ring is labile and self-eliminating, while β-and γ-trifluoromethyl groups in pyridine liberate one fluorine atom at the fission of of carbon-fluorine bond. It seems interesting, therefore, to compare the results of the nucleophilic reactions with those of the mass spectra.

We chose sodium ethoxide and hydroxide to serve as nucleophiles and examined S_N reactions in ethanol. First, (trifluoromethyl) quinolines were refluxed in ethanol with sodium ethoxide. While 2-and 4-isomers (I and III) were recovered, 3-isomer(II) gave 3-(triethoxymethyl) quinoline, which was converted to ethyl 3-quinoline carboxylate (VII) on passing through aluminium oxide column. These results show that this reaction does not proceed through S_N2 mechanism as with type 2, since I and III should be more reactive than II in type 2 reaction. When I, II, and III were refluxed in ethanol with sodium hydroxide, all the starting materials were recovered. Therefore, the reaction mixtures in a sealed glass tube were heated at a higher temperature than above and the corresponding carboxylic acid was obtained in a high yield. Benzotrifluoride was recovered in this condition, which shows that the quinoline ring is indispensable for the hydrolysis, namely, the electron attracting effect of quinoline ring favors the S_N reaction of type 2.

Generally, N-oxidation of aromatic amines markedly changes their reactivities and it seemed interesting to examine the SN reactions of (trifluoromethyl) quinoline N-oxides. First, 2-, 3-, and 4-(trifluoromethyl) quinoline 1-oxide (IV, V, and VI) were refluxed in ethanol with sodium ethoxide. Again, 2-and 4-isomers were recovered, while 3-isomer gave ethyl 3-quinolinecarboxylate (VII) after reduction of the N-oxide group. Next, IV, V, and VI were heated in ethanol with sodium ethoxide at a higher temperature than above in sealed tubes and the corresponding esters with reduction of N-oxide groups were obtained. In these experiments, we could not observe the effects of N-oxide group, but results from the reduction of N-oxide with alkoxide prompted us to examine whether it generally takes place.

TABLE I

Starting material	Condition	Product	Yield (%)
2-CF_3-quinoline (I)	A	——[a]	—
3-CF_3-quinoline (II)	A	ethyl 3-quinolinecarboxylate (VII)[b]	85[b]
4-CF_3-quinoline (III)	A	——[a]	
I	B	quinalidic acid	74
II	B	3-quinolinecarboxylic acid	73
III	B	cinchonic acid	86
N-Oxide of I (IV)	A	——[a]	—
N-Oxide of II (V)	A	VII[b]	83[b]
N-Oxide of III (VI)	A	——[a]	—
IV	C	ethyl quinaldate[b]	32[b]
V	C	VII	62[b]
VI	C	ethyl cinchonate[b]	58[b]

A) NaOEt in EtOH, reflux 3 hr
B) Alc. NaOH in tube, 120—130°, 8 hr
C) NaOEt in EtOH, 120—130°, 5 hr
a) The starting material was recovered.
b) Isolation and identification were carried out as picrates.

7) Y. Kobayashi, E. Nakano, and E. Chinen, *Chem. Pharm. Bull.* (Tokyo), **15**, 1901 (1967).

Pyridine, quinoline, and isoquinoline N-oxides were heated with sodium ethoxide(or methoxide) in ethanol (or methanol) in sealed tubes and gave the corresponding basesni high yields. Miyano, *et al.*[8] reported that N-oxide group is reduced with benzyl alcohol and alkali, but our result shows that reduction is not specific to benzyl alcohol and that lower alcoxides also reduce N-oxide group under a drastic condition. The above results are shown in Tables I and II.

Table II. Yields (%) of Free Base by Reduction with ROH–RONa

N-Oxide	Condition	
	EtOH–NaOEt	MeOH–NaOMe
Pyridine	75	69
Quinoline	77	85
Isoquinoline	96	85

All the yields were evaluated as picrates.

The extraordinarily high reactivity of 3-isomer (II) may be interpreted by considering the electronic effect of trifluoromethyl group and the nitrogen atom in the ring in the course of the type 1 mechanism as shown in Chart 2.

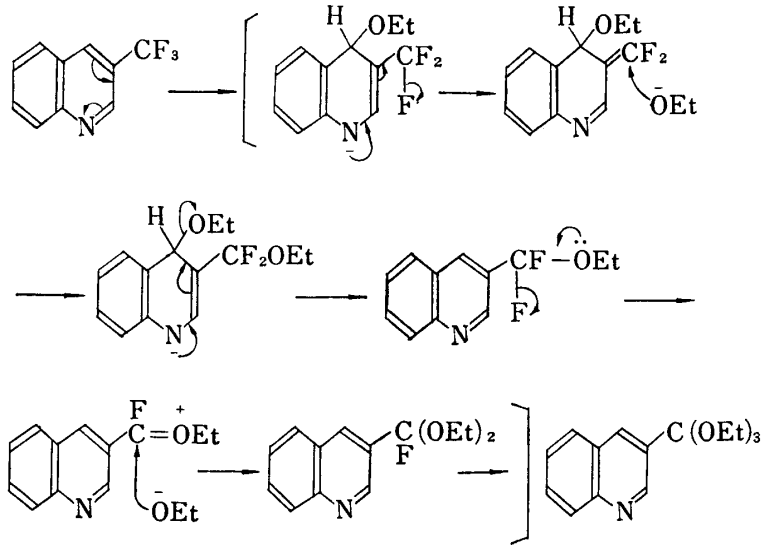

Chart 2

The first step is the attack of ethoxide anion on the electron-deficient 4-position of the quinoline ring: since the back-polarization from nitrogen anion makes carbon-fluorine bond labile, the other ethoxide ion attacks the ω-carbon atom and the first ethoxide anion leaves 4-position. The second and third replacements of fluorine atoms by ethoxy groups may be favored by the lone-pair electrons of the oxygen atom in the ethoxy group. The first step would be comparable to the fact that the lone-pair electrons of nitrogen atoms in the phenothiazine ring facilitates the alcoholysis of trifluoromethyl group.[9] The primary production of 3-(triethoxymethyl) quinoline was observed in nuclear magnetic resonance (NMR) spectrum, but, since it is very labile, all the products were identified after hydrolysis to the ester.

8) S. Miyano, *Chem. Pharm. Bull.* (Tokyo), **14**, 6631 (1966).
9) A. J. Saggiomo, M. Asai, and P. M. Schwartz, *J. Heterocyclic Chem.*, **6**, 631 (1969).

The greater reactivities of I and III than that of benzotrifluoride may be attributed to the electron-attracting effect of the nitrogen atom in the ring.

In the above experiments, we could not find any product through the type 3 mechanism, although it was expected from the data of mass spectra. Our next report will show the type 3 reaction and further results in support of the type 1 mechanism mentioned above.[10]

Experimental

Ethanolysis of 3-(Trifluoromethyl) quinoline (II) by Method A in Table I——3- (Trifluoromethyl) quinoline (300 mg) was dissolved in EtOH (20 ml) contaning Na (0.3 g) and the solution was refluxed for 3 hr and concentrated *in vacuo*. The residue was dissolved in ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over Na_2SO_4 and on evaporation of CH_2Cl_2 a yellow oil was given (NMR ($CDCl_3$): τ 6.58 (6H, quartet), 8.79 (9H, triplet)). This oil was dissolved in $CHCl_3$ and the solution was passed through Al_2O_3 column. The effluent was dissolved in MeOH and picric acid–MeOH solution was added to give 560 mg of picrate, mp 181—182°, which was identified with authentic ethyl 3-quinolinecarboxylate (VII) picrate.

Ethanolysis of 3-(Trifluoromethyl) quinoline 1-Oxide (V) by Method A in Table I——V (300 mg) was treated as I. The CH_2Cl_2 solution was concentrated and passed through Al_2O_3 column. The first effluent gave II (9 mg), the second gave V (10 mg), and the third gave a yellow oil (163 mg), which was identified with VII as picrate.

Hydrolysis of 2-(Trifluoromethyl) quinoline (I) by Method B in Table I——I (1 g) was heated with 10% alc. NaOH (10 ml) in a sealed tube at 120—130° for 8 hr. The cooled tube was opened and the reaction mixture was poured on ice; the tube was rinsed with EtOH and H_2O. The combined solution was evaporated *in vacuo*, the residue was dissolved in H_2O (10 ml), and the solution was acidified by AcOH. To this solution, sat. Pb $(OAc)_2$ was added. The precipitated Pb salt was collected and washed with H_2O. H_2S was passed into the suspension of the above salt. After filtration of PbS, the filtrate was evaporated *in vacuo* to give colorless powder (0.65 g), which was identified with the authentic quinaldic acid by comparing infrared (IR) spectra and mixture melting point.

Hydrolysis of II by Method B in Table I——II (1 g) was treated as I. From the acidified solution, colorless precipitate (0.64 g), mp 275°, was obtained (addition of Pb $(OAc)_2$ solution gave no precipitate). This precipitate was almost pure and identified with the authentic 3-quinoline carboxylic acid by comparing IR spectra and mixture melting point.

Hydrolysis of 4-(Trifluoromethyl) quinoline (III) by Method B in Table I——III (1 g) was treated as II. From the acidified solution, colorless precipitate (0.75 g), mp 257—258°, was obtained. This was identified with the authentic cinchonic acid by comparing IR spectra and mixture melting point.

Ethanolysis of 2-(Trifluoromethyl) quinoline 1-Oxide (IV) by Method C in Table I——IV (300 mg) was heated in NaOEt–EtOH (10 ml) containing Na (0.5 g) at 120—130° for 5 hr in a sealed tube. The cooled tube was opened and treated by method A as in the case of II. The effluent was derived to picrate as usual. Yellow needles (190 mg), mp 153—154°, were obtained, which were identified with ethyl quinaldate picrate by comparing IR spectra and mixture melting point.

Ethanolysis of V by Method C in Table I——V (300 mg) was treated as above and gave yellow needles of picrate (375 mg), mp 181—182°, which were identified with the picrate of VII by comparing IR sepctra and mixture melting point.

Ethanolysis of 4-(Trifluoromethyl) quinoline 1-Oxide (VI) by Method C in Table I——VI (300 mg) was treated as above and gave yellow needles of picrate (350 mg), mp 182—182.5°, which were identified with ethyl cinchonate picrate by comparing IR spectra and mixture melting point.

Reduction of N-Oxides with Sodium Alcoxide——A typical procedure is as follows. Pyridine 1-oxide (2 g) was heated with 10% MeONa–MeOH (20 g) in a sealed tube at 120—130° for 5 hr. After cooling the tube was opened and the reaction mixture was acidified with conc. HCl and concentrated *in vacuo*.

The residue is treated with conc. K_2CO_3 and extracted with $(C_2H_5)_2O$. The $(C_2H_5)_2O$ layer was dried over K_2CO_3 and sat. picric acid–$(C_2H_5)_2O$ was added to the solution to give yellow needles (4.5 g), which were identified with pyridine picrate by mixture melting point.

The other N-oxides in Table II were also reduced by the same procedure as above in MeOH or EtOH and the free bases were identified as their picrates. The yields of the free bases are shown in Table II.

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10) About these facts, a short communication was published by us in *Tetrahedron Letters*, **1970**, 3901.