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Synthesis and Reaction of 3-Fluoro-4-nitroquinoline 1-Oxide[1]

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3-Fluoroquinoline 1-oxide, which was prepared through the Schiemann reaction of 3-aminoquinoline, followed by N-oxygenation, was nitrated to 3-fluoro-4-nitroquinoline 1-oxide. The fluorine atom of this compound was replaced with nucleophiles such as OR- or NR_2-containing compounds in neutral or alkaline media to afford 3-substituted 4-nitroquinoline 1-oxide derivatives. The reaction with aqueous hydrogen chloride brought about the replacement of the nitro group to give 3-fluoro-4-chloroquinoline 1-xoide.

Many 4-nitroquinoline 1-oxide derivatives have been synthesized in several laboratories in view of the carcinogenic and carcinostatic activities of this group of compounds.[3-13] It is well known that this group of compounds are distinguished from their position isomers of nitroquinoline 1-oxides by the ready replacement of the nitro group with various nucleophiles such as -SR, -OR, $-NR_2$, -X,[14] and even with a hydride anion.[15] Polarographic data revealed, as we reported previously,[16] that the nitro group of 4-nitroquinoline derivatives is overwelmingly most susceptible to the electrolytic reduction, which involves the nucleophilic attack by an electron, among other position isomers of nitroquinolines and their 1-oxides. Much attention had been paid at one time to the susceptibility of these derivatives toward such nucleophiles as SH-compounds present in tissue of animals in connection with their carcinogenic activity,[17-21] although general trend of interest at present is toward 4-hydroxyamino

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2) Location: *Tsukiji, Chuo-ku, Tokyo.*
3) Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* (Tokyo), **15**, 1 (1967).
4) M. Hamana and T. Nagayoshi, *Chem. Pharm. Bull.* (Tokyo), **14**, 319 (1966).
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13) H.J. Richter and N.E. Rustad, *J. Org. Chem.*, **29**, 3381 (1964).
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15) Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* (Tokyo), **13**, 1103 (1965).
16) M. Tachibana, S. Sawaki, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **15**, 1112 (1967).
17) H. Endo, *Gann*, **49**, 151 (1958).
18) W. Nakahara and F. Fukuoka, *Gann*, **50**, 1(1959).
19) T. Okamoto and M. Itoh, *Chem. Pharm. Bull.* (Tokyo), **11**, 785 (1963).
20) Y. Hayashi, *Gann*, **50**, 219 (1959).
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derivatives, metabolically produced from 4–nitroquinoline 1–oxides, as the active form in the carcinogenesis of this group of carcinogens.

The present paper describes the synthesis and reactions of 3–fluoro–4–nitroquinoline 1–oxide which is somewhat different in reactivity toward nucleophiles from other 4–nitroquinoline 1–oxides which have so far been studied. This work was undertaken to obtain such a reagent for chemical modification of peptides, proteins and sulfur containing constituents of nucleic acid and related nucleosides and nucleotides, as dinitrofluorobenzene used widely for this purpose, as one of a serial study of "Synthetic Nucleosides and Nucleotides" by one of us (M. S.).

Results and Discussion

3–Fluoroquinoline, the starting material for the present synthetic purpose, was prepared from 3–aminoquinoline *via* quinoline–3–diazonium fluoroborate in analoguous way to the Schiemann reaction of aminopyridine.[22] 3–Fluoroquinoline was readily converted into its N–oxide (mp 111—112°) by heating with hydrogen peroxide in acetic acid in an usual way. The N–oxide thus prepared was nitrated with potassium nitrate in 79% sulfuric acid to give 3–fluoro–4–nitroquinoline 1–oxide (mp 164—165°) in an almost quantitative yield. The selective attack of nitronium ion to 4–position may be due to the strong electron–donating effect of fluorine atom, the spatial size of which is not so large as to hinder the attack of the reagent sterically.

Experiments were undertaken to investigate the reactivity of 3–fluoro–4–nitroquinoline 1–oxide toward nucleophiles. With all 4–nitroquinoline 1–oxides that have so far been studied, it is known that nucleophilic replacement readily occurs at 4–position by treatment with SH, NH, OH, and halogeno compounds to result in liberation of the nitro group and introduction of the nucleophilic reagent moiety. In contrast, two types of replacement reactions of 3–fluoro derivative, which lead to the replacement of either the nitro group or fluorine atom, can be expected in principle to be brought about by the attack of nucleophiles.

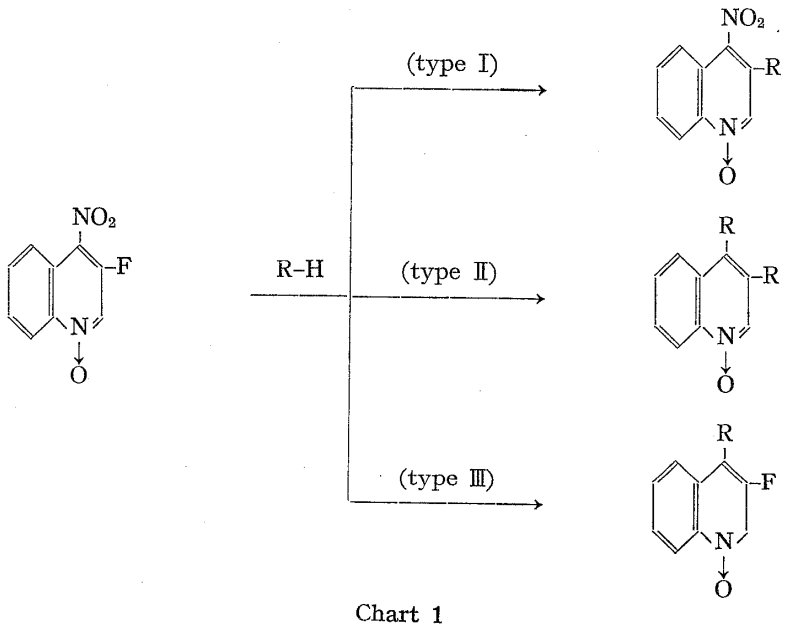
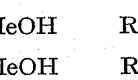


Chart 1

22) 2,5,6,7, and 8–Monofluoroquinoline were already prepared according to the Schiemenan's method.[23]
23) *Org. Reactions*, **5**, 206.

Table I

Type[a]	Reagent	Solvent	Temp.[b] (°C)	Time (min)	R	mp of product
I	28% NH_3	H_2O	60	15	$-NH_2$	218° (decomp.)
I	piperidine	MeOH	R.T.	20		167.5°
I	Ph–NH_2	MeOH	R.T.	60	–NH–Ph	164—165°
I	$NH_2CH_2CH_2OH$	H_2O	R.T.	300	$-NHCH_2CH_2OH$	211° (decomp.)
I	NH_2CH_2COOH	MeOH[c]	R.T.	60	$-NHCH_2COOH$	205° (decomp.)
I	Ph–$NHNH_2$	EtOH	R.T.	30	–NHNH–Ph	138° (decomp.)
I	$NaOCH_3$	MeOH	R.T.	(24 hr)	$-OCH_3$	196°
II	$HSCH_2COOH$	H_2O[c]	R.T.	(24 hr)	$-SCH_2COOH$	208° (decomp.)
III	conc. HCl	H_2O	65	30	–Cl	168—169°

a) Refer to Chart 1. *b*) R.T.=room temperature *c*) Neutralized with $NaHCO_3$ to *ca.* pH 7.

The nucleophilic reagents used in the present study were sodium methoxide, aqueous ammonia, ethanolamine, piperidine, aniline phenylhydrazine,[24] glycine, thioglycolic acid, and aqueous hydrogen chloride. The results are summarized in Chart 1 and Table I. The points to be noted are that, with one exceptional case, the fluorine at 3–position is more reactive than the nitro at 4–position and that further replacement at 4–position required a more drastic condition. With thioglycolic acid, two moles of the reagent were replaced to give 3,4–disubstituted derivative even at room temperature. Only one exceptional case was found in the reaction with hydrogen chloride, where 4–nitro group replaced by a chlorine atom, the fluorine atom remaining intact in the molecule to give 3–fluoro–4–chloroquinoline 1–oxide. The reverse order in the reactivity shown in this case can be reasonably elucidated by the fact that the fluorine atom at 3–position is more reactive, indeed, in neutral or alkaline media, whereas the nitro group in position in γ to the N–oxide is much more activated than the fluorine atom in β–position by the electron–withdrawing effect of the N–oxide group enhanced by protonation in a strong acid medium.

The structures of the replacement products were determined by the elemental analytica data and by proving the presence or absence of a nitro group using the polarograph method. 3–Methoxy–4–nitroquinoline 1–oxide was identified with the authentic sample, which was prepared through the nitration of 3–methoxyquinoline 1–oxide, by the mixed melting point test and infrared spectroscopy.

Among the fluorine compounds reactive toward nucleophiles, 2,4–dinitrofluorobenzene is the best known to readily undergo the replacement of fluorine atom with nucleophiles, so that this compound is of great practical use for chemical modification of peptides, protein, and so on. 3–Fluoro–4–nitroquinoline 1–oxide may be applicable to this kind of purpose in addition to the synthetic purpose for 3,4–disubstituted quinoline derivatives. Selective chemical modification of various biological substances, *e.g.* functional studies of transfer RNA,[29] with this compound might be worth doing. As a preliminary study along this line, qualitative comparisons were made in the reaction rates of 3–fluoro–4–nitroquinoline 1–oxide and 2,4–dinitrofluorobenzene with 0.1% glycine solution in phosphate buffer (pH 7.51) at 30°. The reaction process was traced by measuring an increase in the ultraviolet absorption

24) Under the same reaction condition as chosen in the present study, 4–nitroquinoline 1–oxide derivatives are known to be readily reduced to the corresponding 4–hydroxyaminoquinoline 1–oxides.[3,25–28]

25) E. Ochiai and H. Mitarashi, *Chem. Pharm. Bull.* (Tokyo), **11**, 1084 (1963).
26) E. Ochiai and H. Mitarashi, *Ann. Rept. ITSUU Lab.*, **13**, 19 (1963).
27) E. Ochiai and H. Mitarashi, *Ann. Rept. ITSUU Lab.*, **14**, 17 (1964).
28) Y. Kawazoe and M. Araki, *Chem. Pharm. Bull.* (Tokyo), **16**, 839 (1968).
29) M. Saneyoshi and S. Nishimura, *Biochim. Biophys. Acta*, **145**, 208 (1967).

at around 470 mμ or 360 mμ which is due to the formation of 3–carboxymethylamino–4–nitroquinoline 1–oxide or 2,4–dinitrophenylglycine. The rates were found to be 1.4×10^{-5} and 4.3×10^{-5} mole/sec for 3–fluoro–4–nitroquinoline 1–oxide and 2,4–dinitrofluorobenzene, respectively.[30]

Experimental

3-Fluoroquinoilne 1-Oxide——Twenty–four grams of anhydrous H_3BO_3 and 70 g of 46% HF were mixed in a teflon flask under ice–cooling. The resulting 41% HBF_4 was added to 150 ml of the 95% EtOH solution containing 12.5 g of 3–aminoquinoline with mechanical stirring under ice–cooling. To this mixture was gradually added 33 g of *n*–amyl nitrite and the reaction mixture was kept at 0° with stirring, when a considerable amount of precipitate came out. To this suspension was added 50 ml of ether and the precipitates were collected on a filter, washed with 300 ml of ether and then with *n*–hexane. The precipitates were kept wet with solvent throughout the filtration procedure. The colored precipitates were suspended in 300 ml of *n*–hexane and then, warmed at 50—55°, when N_2 gas was evolved. It took about 10 hr for completion of gas evolution. After addition of 5 ml of conc. HCl, the solvent was evaporated. The residue was made alkaline with aqueous NaOH and destilled with stream. About 1 liter of the destillate was extracted with ether. After ether was evaporated, the residue was destilled under an atomospheric pressure to give *ca.* 10 g of 3–fluoroquinoline. bp 198—200°.

Fifteen grams of the resulting 3–fluoroquinoline was dissolved in 30 ml of CH_3COOH and 10 ml of 30% $H_2O_2$was added. The reaction mixture was kept at 65° for 4 hr. After decomposition of excess of H_2O_2 with PtO_2, the solvent was evaporated under reduced pressure. The residue was extracted with $CHCl_3$. After evaporation of the solvent, 14 g of white grannules were obtained. mp 117—118°. The structure was supposed to be as 3–fluoroquinoline 1–oxide by nuclear magnetic resonance spectroscopy, and determined by deriving it to 3–fluoro–4–nitroquinoline 1–oxide.

3-Fluoro-4-nitroquinoline 1-Oxide——3–Fluoroquinoline 1–oxide (2.5 g) was warmed with 25 ml of 79% H_2SO_4 at 90°. To this soultion, 2 g of KNO_3 was added in small portions during 1 hr. The reaction mixture was kept at 90° for another 3 hr, and then poured into 100 ml of ice water. The resulting precipitate was collected on a filter, washed with H_2O, and dissolved in $CHCl_3$. The $CHCl_3$ extract was washed with saturated aq. $NaHCO_3$ and dried over anhyd. Na_2SO_4. After $CHCl_3$ was evaporated *in vacuo*, yellow residue was recrystallized from MeOH. 3–Fluoro–4–nitroquinoline 1–oxide was obtained as yellow needles, mp 164—165°. Yield, 2.5 g (96.5%). *Anal.* Calcd. for $C_9H_5O_3N_2F$: C, 51.89; H, 2.42; N, 13.45. Found: C, 52.21; H, 2.45; N, 13.29.

3-Amino-4-nitroquinoline 1-Oxide——3–Fluoro–4–nitroquinoline 1–oxide (50 mg) was suspended in 28% aqueous NH_3 and warmed at 60° for 15 min. Orange needles which formed were collected on a filter and washed with water to 35 mg of pure 3–amino–4–nitroquinoline 1–oxide, mp 218° (decomp.). Yield, 71%. *Anal.* Calcd. for $C_9H_7O_3N_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.77; H, 3.05; N, 20.86.

3-Piperidino-4-nitroquinoline 1-Oxide——To a solution of 50 mg of 3–fluoro–4–nitroquinoline 1–oxide in 1 ml of MeOH, was added 0.5 ml of piperidine dropwise. The reaction mixture was kept standing at room temperature under stirring for 20 min. The resulting orange needles were collected and recyrstallized from MeOH to 28 mg of 3–piperidino–4–nitroquinoline 1–oxide, mp 167.5°. Yield, 43%. *Anal.* Calcd. for $C_{14}H_{15}O_3N_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.37; H, 5.53; N, 15.42.

3-Anilino-4-nitroquinoline 1-Oxide——A solution of 50 mg of 3–fluoro–4–nitroquinoline 1–oxide in 2 ml of MeOH was stirred with 0.5 ml of aniline at room temperature for 1 hr. The resulting reddish orange needles were collected by filtration to 51.5 mg of almost pure 3–anilino–4–nitroquinoline 1–oxide, mp 164—165.5°. Yield, 75%. *Anal.* Calcd. for $C_{15}H_{11}O_3N_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.82; H, 4.23; N, 15.11.

3-(2-Hydroxyethylamino)-4-nitroquinoline 1-Oxide——3–Fluoro–4–nitroquinoline 1–oxide (50 mg) was mixed with 0.5 ml of H_2O and 0.5 ml of ethanolamine and the mixture was kept standing at room temperature for 5 hr. The resulting orange precipitate was collected on a filter, washed with MeOH, and recrystallized from MeOH. The yield was quantitative. mp 211° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}O_4N_3$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.70; H, 4.43; N, 16.79.

3-Carboxymethylamino-4-nitroquinoline 1-Oxide——A mixture of 50 mg of 3–fluoro–4–nitroquinoline 1–oxide, 40 mg of glycine, and 45 mg of $NaHCO_3$ was stirred in 10 ml of MeOH at room temperature for 1 hr. After addition of water, the pH of the reaction mixture was adjusted to 3.0 with aq. HCl. The resulting yellow precipitate was collected and recrystallized from MeOH, mp 200.5° (decomp.). Yield, 48 mg (76%). *Anal.* Calcd. for $C_{11}H_9O_5N_3$: C, 50.19; H, 3.45; N, 15.97. Found: C, 50.24; H, 3.49; N, 15.89.

30) These values were calculated as a pseudo–first order reaction rate, since the concentration of glycine was hundred times larger than that of 3–fluoro–4–nitroquinoline 1–oxide.

3-Phenylhydrazino-4-nitroquinoline 1-Oxide——A mixture of 200 mg of 3–fluoro–4–nitroquinoline 1–oxide, 5 ml of EtOH, and 0.5 ml of phenylhydrazine was stirred at room temperature for 30 min. The resulting orange needles were collected on a filter and washed with MeOH to almost pure 3–phenylhydrazino–4–nitroquinoline 1–oxide (225 mg), mp 138° (decomp.). Yield, 79%. *Anal.* Calcd. for $C_{15}H_{12}O_3N_4$: C, 60.80; H, 4.08; N, 18.91. Found: C, 61.06; H, 4.05; N, 18.71.

3-Methoxy-4-nitroquinoline 1-Oxide——In 5 ml of cooled MeOH was dissolved 100 mg of metallic Na, and then 50 mg of 3–fluoro–4–nitroquinoline 1–oxide. The mixture was stirred at room temperature for 24 hr. The resulting yellow precipitate was collected on a filter, washed with MeOH, and recrystallized from MeOH. The material thus obtained (27 mg) was identified with the authentic sample of 3–methoxy–4–nitroquinoline 1–oxide. Yield, 51%.

3,4-Bis(carboxymethylthio)quinoline 1-Oxide——3–Fluoro–4–nitroquinoline 1–oxide (50 mg) was suspended in 2 ml of H_2O containing 0.5 ml of thioglycolic acid. The mixture was neutralized to pH 7.0 with $NaHCO_3$ and kept standing at room temperature for 24 hr. Acidification of the reaction mixture with aqueous HCl to pH 3.0 yielded the precipitate which was collected by centrifugation and recrystallized from MeOH, mp 208° (decomp.). Yield, 43 mg (50%). *Anal.* Calcd. for $C_{13}H_{11}O_5NS_2$: C, 48.01; H, 3.41; N, 4.31. Found: C, 47.61; H, 3.59; N, 4.01.

3-Fluoro-4-chloroquinoline 1-Oxide——3–Fluoro–4–nitroquinoline 1–oxide (50 mg) was dissolved in 1 ml of conc. HCl and warmed at 65° for 30 min. The reaction mixture was neutralized with Na_2CO_3 and extracted with $CHCl_3$. $CHCl_3$ was evaporated *in vacuo* and the white residue was recrystallized from MeOH to white needles. *Anal.* Calcd. for C_9H_5ONClF: C, 54.66; H, 2.53. Found: C, 54.46; H, 2.53.

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