[Chem. Pharm. Bull. 16(5) 839—847 (1968)]

UDC 615.771.7-011 : 547.831.6.04

Studies on Chemical Carcinogens. VI.[1] Reductions of 3- and 8-Substituted 4-Nitroquinoline 1-Oxides

Yutaka Kawazoe and Misako Araki (née Tachibana)

National Cancer Center Research Institute[2]

(Received July 6, 1967)

Reductions of 3- and 8-substituted 4-nitroquinoline 1-oxides with H_2/Pd-C, $NaBH_4$, and phenylhydrazine were examined. These compounds were proved to be easily deoxygenated to produce the corresponding 4-hydroxyaminoquinolines in contrast to the fact that many other substituted 4-nitroquinoline 1-oxides were reduced to 4-hydroxyaminoquinoline 1-oxides under the same reduction conditions. These reductive behaviors were discussed in connection with the polarographic reduction potentials and the carcinogenic activity of these compounds.

It is well known that 4-nitroquinoline 1-oxide (I) and one of its reduction products, 4-hydroxyaminoquinoline 1-oxide (II), are potent carcinogens.[3-7] In our previous work,[8,9] the syntheses of substituted 4-nitroquinoline 1-oxides and their corresponding 4-hydroxyamino derivatives and the carcinogenicity of these compounds were studied for finding out the relationship between the carcinogenic activity and the chemical structure. This paper reports, as a further study in this connection, the reduction of 3- and 8-substituted 4-nitroquinoline 1-oxides, which react with reducing agents somewhat differently from 2-, 5-, 6-, and 7-substituted 4-nitroquinoline 1-oxides.

Results and Discussion

4-Nitroquinoline 1-oxide (I) and its derivatives having another substituent on positions 2, 5, 6, and 7 undergo a stepwise catalytic reduction over palladium-charcoal to give the corresponding 4-hydroxyamino 1-oxides, 4-amino 1-oxides, and then 4-aminoquinolines, successively, as far as the compounds we studied are concerned.[8] The reduction by phenylhydrazine, on the other hand, stops at the stage of the corresponding hydroxyamino derivatives and this method seems to be the most convenient way for preparation of 4-hydroxyamino 1-oxide derivatives.[10-12] Furthermore, as we reported previously, sodium borohydride reduction of 4-nitroquinoline 1-oxide yields 4-hydroxyaminoquinoline 1-oxide (II) in 30% yield, besides denitrated quinoline 1-oxide and deoxygenated 4-nitroquinoline as the main by-products.[13] In contrast to these results, 3- and 8-substituted derivatives yielded different

1) Part V: *Gann*, **58**, 485 (1967).
2) Location: *Tsukiji, Chou-ku, Tokyo.*
3) W. Nakahara, F. Fukuoka, and T. Sugimura, *Gann*, **48**, 129 (1957).
4) W. Nakahara, F. Fukuoka, and S. Saki, *Gann*, **49**, 33 (1958).
5) W. Nakahara, *Arzneimittel Forsch.*, **14**, 842 (1962).
6) Y. Shirasu, *Gann*, **54**, 487 (1963).
7) H. Endo, *Gann*, **54**, 443 (1963).
8) Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* (Tokyo), **15**, 1 (1967).
9) Y. Kawazoe, M. Tachibana, K. Aoki, and W. Nakahra, *Biochem. Pharmacol.*, **16**, 631 (1967).
10) E. Ochai and H. Mitarashi, *Chem. Pharm. Bull.* (Tokyo), **11**, 1084 (1963).
11) E. Ochiai and H. Mitarashi, *Ann. Rept. Itsuu Lab.*, **13**, 19 (1963).
12) E. Ochiai and H. Mitarashi, *Ann. Rept. Itsuu Lab.*, **14**, 17 (1964).
13) Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* (Tokyo), **13**, 1103 (1965).

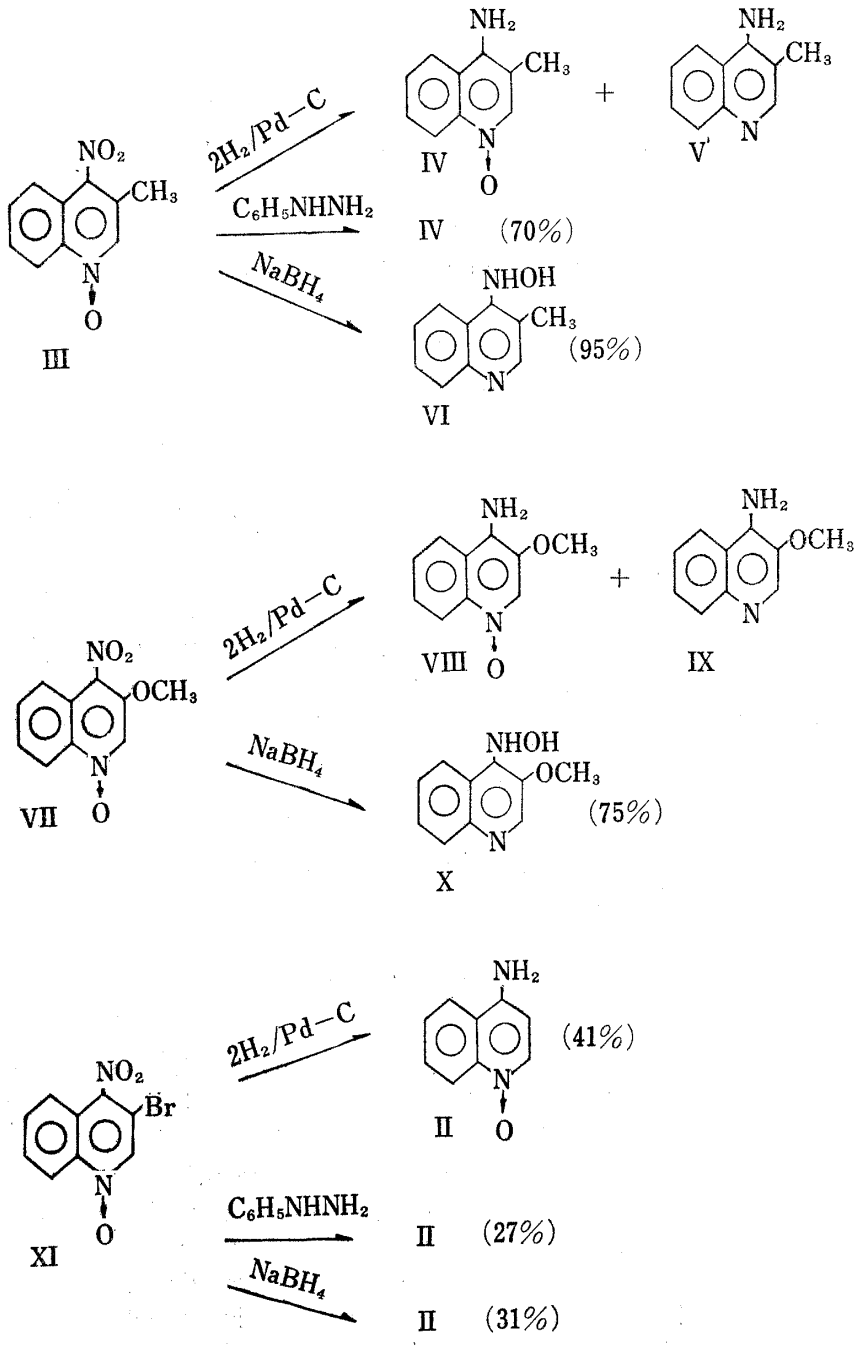

Chart 1

types of reduction products from those produced by other substituted 4–nitroquinoline 1–oxides, as illustrated in Charts 1 and 2.

The catalytic reduction of 3–methyl–4–nitroquinoline 1–oxide (III) gave a mixture of two compounds (IV and V) when just two moles of hydrogen were consumed, no other products being detected in the reduction mixture except for the starting material. Compound III reacted with phenylhydrazine in ethanol to give a yellow precipitate (IV, mp 242—243°) in 70% yield, but sodium borohydride reduction of III yielded a different product of colorless crystals (VI, mp 155—156°) in 95% yield. Products IV and VI thus obtained showed the same elemental composition of $C_{10}H_{11}ON_2$ and both compounds absorbed one mole of hydrogen to yield a common product of 3–methyl–4–aminoquinoline (V) which was identified with the ultimate catalytic reduction product of the parent nitro compound (III). Nuclear mag-

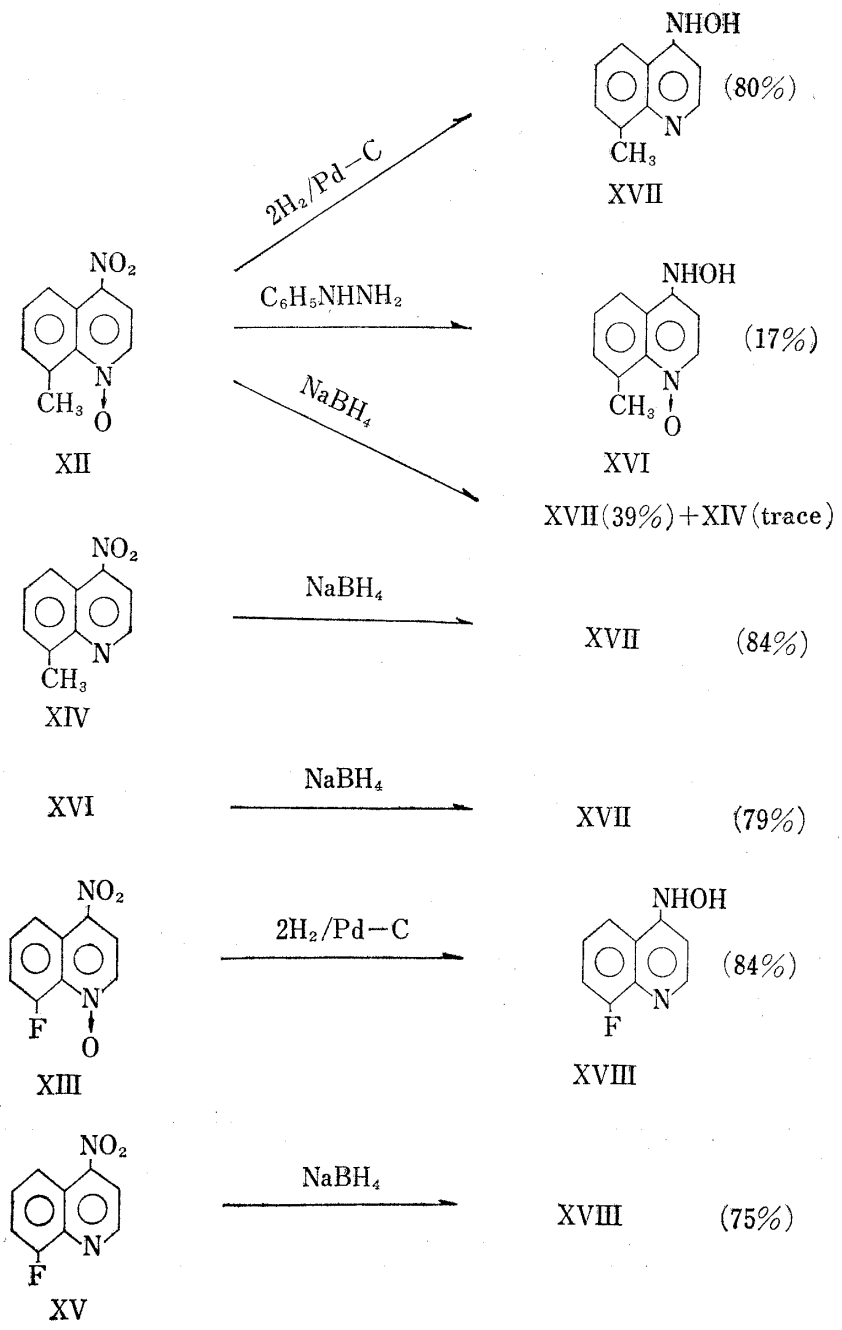

Chart 2

netic resonance spectroscopy provided a clear solution for the structures of IV and VI. Thus, the signal of proton-2 of VI appeared as a doublet in acidic solution, indicating the presence of $\rangle N^+$–H function in the molecule because this splitting disappeared when the acid medium was replaced by a deuterated one. On the other hand, proton-2 signal of IV appeared as a singlet even in strongly acidic medium, suggesting the presence of $\rangle N^+$–OH function in acidic medium instead of $\rangle N^+$–H. As a result, the structures of IV and VI were definitely established as 3-methyl-4-aminoquinoline 1-oxide and 3-methyl-4-hydroxyaminoquinoline, respectively.

Very similar behavior was observed with 3-methoxy-4-nitroquinoline 1-oxide (VII), as shown in Chart 1. Thus, 4-hydroxyaminoquinoline 1-oxide derivative could not be isolated by interruption of the catalytic hydrogenation of VII at the stage when two moles of hydrogen was absorbed. The products isolated were 3-methoxy-4-aminoquinoline (IX) and its 1-oxide (VIII). Sodium borohydride reduction of VII, on the other hand, yielded another product X (mp 105° (decomp.), $C_{10}H_{10}O_2N_2$) which catalytically absorbed one mole

of hydrogen to form 3–methoxy–4–aminoquinoline (IX). The structure of X could, therefore, be assumed as 3–methoxy–4–hydroxyaminoquinoline as shown in Chart 1. Compound VII reacted with phenylhydrazine at around 80° and yielded many unidentifiable products, the details being open to further investigation.

As described above, the marked difference in the reduction reactions of these 3–substituted derivatives, III and VII, from those of many other 4–nitroquinoline 1–oxides is not to produce 4–hydroxyaminoquinoline 1–oxides but to produce deoxygenated 4–hydroxyaminoquinolines.

3–Bromo–4–nitroquinoline 1–oxide (XI) was debrominated, simultaneously or prior to reduction of the nitro group, to produce 4–hydroxyaminoquinoline 1–oxide (II) by either phenylhydrazine or sodium borohydride, the yield being 27% and 31%, respectively. Catalytic reduction of XI produced debrominated 4–aminoquinoline 1–oxide in 42% yield and any bromoquinoline derivatives were not isolated from the reduction mixture after two moles of hydrogen was catalytically absorbed.

With 8–substituted 4–nitroquinoline 1–oxides, it may be expected that 1–oxide group is sterically hindered by a substituent at position 8, so that the deoxygenation may easily occur. As a matter of fact, when 8–methyl– and 8–fluoro–quinoline 1–oxides were nitrated in usual way, a considerable amount of deoxygenated 8–substituted 4–nitroquinolines (XIV and XV) were produced (5% and 10%, respectively), whereas deoxygenated compounds were not obtained from nitration of other quinoline 1–oxide derivatives unless the reaction temperature was raised much higher than 100°. The reduction of these compounds are illustrated in Chart 2. Among fifteen 4–nitroquinoline 1–oxides, whose reduction reactions has been examined,[6] 8–methyl derivatives (XII) is the only example where both types of reduction products, 8–methyl–4–hydroxyaminoquinoline (XVII) and its 1–oxide (XVI), were isolated from the reductions above–described. Thus, XVI was obtained in 17% yield by phenylhydrazine reduction, as reported in our preceding paper.[8] The sodium borohydride reduction of XII, on the other hand, gave colorless crystals (XVII, $C_{10}H_{10}ON_2$) in 39% yield. This product (XVII) absorbed one mole of hydrogen catalytically and its NMR signal of proton–2 was changed from doublet to a triplet by the addition of an acid. This means that sodium borohydride reduction brought about deoxygenation of the N–oxide group. As a result, XVII was identified as 8–methyl–4–hydroxyaminoquinoline. Product XVII was also produced by sodium borohydride reduction of 8–methyl–4–hydroxyaminoquinoline 1–oxide (XVI) and 8–methyl–4–nitroquinoline (XIV) in 84% and 79% yield, respectively. It is to be noted that with 8–methyl derivatives (XII), 8–methyl–4–aminoquinoline 1–oxide has not yet been isolated by the reduction methods we studied.

The catalytic reduction of 8–fluoro–4–nitroquinoline 1–oxide (XIII) yielded 8–fluoro–4–hydroxyaminoquinoline (XVIII) in a good yield, which was identified with the product

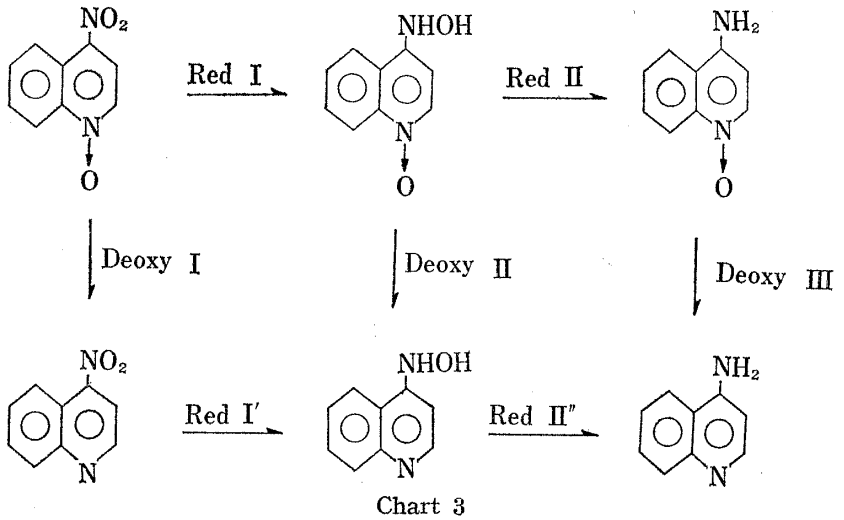

Chart 3

Table I. Polarographic Half-Wave Reduction Potentials of Nitro-, Hydroxyamino-, and Amino-quinoline Derivatives measured in Aqueous Buffer Solutions at Various pH's at 25°

	pH	Red I[a]	Red II	Deoxy III	Deoxy I	Red I′	Red II′
4NQO (I)	4.00	−0.185	−0.800	−1.055			
	7.06	−0.160	−0.975	−1.245			
	8.62	−0.24	−1.07	−1.36			
4HAQO (II)	4.00		−0.800	−1.060			
	7.06		−0.970	−1.240			
	8.62		−1.070	−1.37			
4AQO	4.00			−1.060			
	7.06			−1.235			
	8.62			−1.37			
4NQ	4.00					−0.080	−0.850
	7.06					−0.195	−0.880
	8.62					−0.255	−1.030
3-Me-4NQO (III)	4.00	−0.200	−0.705	−1.135			
	7.06	−0.275	?	−1.230			
	8.62	−0.360	?	−1.385			
3-Me-4AQO (IV)	4.00			−1.135			
	7.06			−1.225			
	8.62			−1.350			
3-Me-4HAQ (VI)	4.00						−0.750
	7.06						−0.675
	8.62						−0.770
3-OMe-4NQO (VII)	4.00	−0.115 (Other waves have not yet been assigned.)					
	7.06	−0.260 (Other waves have not yet been assigned.)					
	8.62	−0.360 (Other waves have not yet been assigned.)					
3-OMe-4AQO (VIII)	4.00			−0.910			
	7.06			−1.115			
	8.62			−1.230			
3-OMe-4HAQ (X)	4.00						−0.530
	7.06						−0.610
	8.62						−0.710
8-Me-4NQO (XII)	4.00				±0.0	−0.070	−0.800
	7.06				−0.12	−0.19	−0.865
	8.62				−0.2	−0.265	−0.960
8-Me-4NQ (XIV)	4.00					−0.075	−0.805
	7.06					−0.195	−0.865
	8.62					−0.250	−0.960
8-Me-4HAQ (XVII)	4.00						−0.820
	7.06						−0.860
	8.62						−0.975
8-Me-4HAQO (XVI)	4.00		−0.770[b]	−0.770[b]			
	7.06		−0.880[b]	−0.880[b]			
	8.62		−0.950[b]	−0.950[b]			
8-F-4NQO (XIII)	4.00				+0.03	−0.050	−0.760
	7.06				−0.05	−0.160	−0.840
	8.62				−0.13	−0.230	−0.965
8-F-4NQ (XV)	4.00					−0.050	−0.760
	7.06					−0.160	−0.840
	8.62					−0.225	−0.945
8-F-4HAQ (XVIII)	4.00						−0.765
	7.06						−0.845
	8.62						−0.960

a) Refer to Chart 3.
b) The alternative assignment of these overlapped waves may be "Deoxy II and Red II'" instead of "Red II and Deoxy III'."

from sodium borohydride reduction of 8–fluoro–4–nitroquinoline (XV), whereas sodium borohydride and phenylhydrazine reduction of XIII gave a mixture of reduction products, the structures of which are now under investigation.

In connection with the chemical reductions described above, the polarographic reduction of these nitro compounds was examined.[14] The assignments of the reduction waves were accomplished by comparison of the polarograms of the partly reduced derivatives such as hydroxyamino, amino, and deoxygenated derivatives. The half–wave potentials obtained in aqueous acidic, neutral, and basic media are summarized in Table I and Chart 3. It is worth noting that both 8–methyl– and 8–fluoro–4–nitroquinoline 1–oxides (XII and XIII) showed the first wave at around 0.0——0.2 volt, attributed to the deoxygenation process prior to the reduction of nitro group. The polarographic data seem to coincide with the chemical behaviors of 8–substituted derivatives toward the reducing agents. Contrary to this, the polarogram of 3–methyl–4–nitroquinoline 1–oxide (III), which yields the corresponding 4–hydroxyaminoquinoline (VI), appeared somewhat complex as shown in Fig. 1. Thus, although in acidic medium it gave the same patterns as that of the parent 4–nitroquinoline 1–oxide (I) (Red I → Red II → Deoxy III), the second wave due to Red II became collapsed in both neutral and alkaline media. The deoxygenation seems to take place under the highest voltage supplied, indicating a disagreement of polarographic data with chemical behavior. It is, furthermore, to be noted that 3–methyl–4–hydroxyaminoquinoline 1–oxide, the synthesis of which has not yet succeeded, might be expected to be obtained by the preparative electrolytic reduction of III in acidic medium.

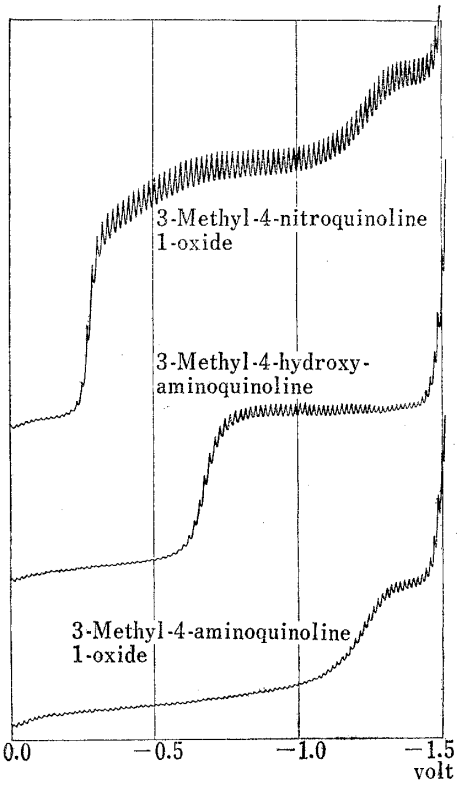

Fig. 1. Polarograms of 3–Methyl–4–nitroquinoline 1–Oxide (III), 3–Methyl–4–hydroxyaminoquinoline (VI), and 3–Methyl–4–aminoquinoline 1–Oxide (IV) measured in the Phosphate Buffer (M/15) at pH=7.06 at 25°

Conclusion

The fact that 3–methyl– and 3–methoxy–4–nitroquinoline 1–oxides did not produce their corresponding 4–hydroxyaminoquinoline 1–oxides but produced deoxygenated 4–hydroxyaminoquinolines by the reduction methods employed in this study might suggest that these 4–hydroxyaminoquinoline 1–oxide derivatives are not stabilized in the presence of reducing agents and that, as a result, further reduction takes place to yield the deoxygenated 4–hydroxyaminoquinolines. The mechanism which is involved in the deoxygenation process affected by a 3–substituent seems not to be clear at present. Thus, a possible explanation that destabilization may be brought about by the 4–nitro and/or hydroxyamino group sterically hindered by a 3–substituent and considerably twisted from the aromatic ring plane appears to be not acceptable, becuase, as we previously reported, 5–methyl–4–nitroquinoline 1–oxide,

14) A comprehensive study on polarographic reduction of sixty nitroquinoline derivatives was already reported.[15]

15) M. Tachibana, S. Sawaki, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **15**, 1112 (1967).

where the nitro group is considered to be more twisted from the aromatic ring plane, is reduced to its corresponding hydroxyaminoquinoline 1-oxide derivative as readily as 4-nitroquinoline 1-oxide itself.

It is of interest, furthermore, in connection with the carcinogenic mechanism of 4-nitroquinoline derivatives that all the 4-nitro derivatives which did not yield the 4-hydroxyaminoquinoline 1-oxide derivatives by reductive ways were proved not to be carcinogenic, whereas those which gave 4-hydroxyaminoquinoline 1-oxide derivatives by the reduction were all carcinogenic. In addition to the above results, because the fifteen 4-hydroxyaminoquinoline 1-oxides which were synthesized from 4-nitro derivatives in our laboratory were all carcinogenic, it is very probable that the production of 4-hydroxyaminoquinoline 1-oxide derivatives is an essential process for the carcinogenic activity of 4-nitroquinoline 1-oxides; in other words, 4-hydroxyaminoquinoline 1-oxide structure must be the active form in the carcinogenesis of this class of carcinogens. The detail on the carcinogenicity-structure relation was and will be published in the literature referred to (9) and the following papers.

It may be worth mentioning at the end of this paper that 5-nitroquinoline 1-oxide (XIX) underwent the reduction reactions to give 5-hydroxyaminoquinoline 1-oxide (XX) which absorbed further two moles of hydrogen over 5% palladium-charcoal catalyst to afford 5-aminoquinoline. In spite of the similarity between 4- and 5-nitroquinoline 1-oxides, the latter compound and its 5-hydroxyamino 1-oxide derivative were proved to be non-carcinogenic. This finding may be of importance for elucidation of the carcinogenic mechanism of carcinogenic quinoline derivatives.

Experimental

Reduction of 3-Methyl-4-nitroquinoline 1-Oxide (III)——i) Catalytic Reduction: A solution of 432 mg of III in 10 ml of EtOH was catalytically hydrogenated over 100 mg of 5% Pd-C catalyst. The reaction was interrupted after absorption of 3.0 moles of H_2 gas. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting yellow residue was chromatographed through Al_2O_3 column, eluting with $CHCl_3$ and then with $CHCl_3$ containing 2% MeOH. From the $CHCl_3$ fraction, 50 mg of 3-methyl-4-aminoquinoline (V) was obtained as white needles which were recrystallized from benzene. mp 130—131°. Yield, 15%. *Anal.* Calcd. for $C_{10}H_{10}N_2 \cdot H_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.86; H, 6.59; N, 15.66.

From the $CHCl_3$–MeOH fraction was obtained 64 mg of 3-methyl-4-aminoquinoline 1-oxide (IV), which was recrystallized from Me_2CO–MeOH. mp 242—243° (decomp.). Yield, 17%. Recrystallization from conc. HCl–MeOH gave its hydrochloride. mp 294—295° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}ON_2Cl$: C, 57.01; H, 5.26; N, 13.30. Found: C, 57.27; H, 5.25; N, 13.30.

ii) With $NaBH_4$: To a suspension of 100 mg of III in 20 ml of a mixture of EtOH and H_2O (1:9 v/v%) in N_2 atmosphere, 1.0 g of $NaBH_4$ was slowly added at 25°. After the mixture was kept standing at this temperature for 6 hr with stirring, the resulting yellow precipitate was collected by filtration, washed with water, and dried. Pale yellow powder thus obtained (81 mg, yield, 95%) was almost pure 3-methyl-4-hydroxyaminoquinoline (VI). mp 155—156° (decomp.). Recrystallization from conc. HCl–MeOH gave its hydrochloride. mp 255—260° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}ON_2Cl$: C, 57.01; H, 5.26; N, 13.30. Found: C, 56.75; H, 5.41; N, 13.16.

iii) With Phenylhydrazine: A mixture of 200 mg of III, 4 ml of EtOH, and 1 ml of phenylhydrazine was gently refluxed for 5 hr. After evaporarion of EtOH and phenylhydrazine *in vacuo*, 4 ml of benzene was added, when brown-yellow precipitate came out. It was collected by filtration, washed with ether, and then dried. Recrystallization from MeOH–Me_2CO gave 118 mg of 3-methyl-4-aminoquinoline 1-oxide (IV). Yield, 69%. White needles of the hydrochloride were obtained by recrystallization from conc. HCl–MeOH. mp 294—295° (decomp.).

Reduction of 3-Methoxy-4-nitroquinoline 1-Oxide (VII)——i) Catalytic Reduction: A solution of 200 mg of VII in 20 ml of EtOH was hydrogenated over 50 mg of 5% Pd-C with stirring at room temperature until the absorption of hydrogen became slow. After removal of the catalyst by filtration and of the solvent by evaporation *in vacuo*, the residue was passed through an Al_2O_3 column, eluting with $CHCl_3$. From the first fraction, 25 mg of 3-methoxy-4-aminoquinoline (IX) was obtained. mp 155°. Yield, 15%. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.06. Found: C, 68.89; H, 5.89; N, 16.06.

From the following fractions, 3-methoxy-4-aminoquinoline 1-oxide (VIII) was obtained. Yield, 62%. mp 226—228° (decomp.). Its hydrochloride melted at 235° (decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_2N_2Cl$ (hydrochloride): C, 52.95; H, 4.85; N, 12.35. Found: C, 52.75; H, 5.05; N, 12.39.

ii) With $NaBH_4$: One gram of $NaBH_4$ was slowly added to a suspension of 200 mg of VII in 10 ml of **EtOH–H_2O** (1:4 v/v%) in N_2 atmosphere at 25°. After 24 hr, the resulting white yellow precipitate was collected by filtration, washed with water, and then dried. Recrystallization from MeOH gave 130 mg of 3–methoxy–4–hydroxyaminoquinoline (X) as yellow scales.[16] mp 105° (decomp.). Yield, 75%. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.22; H, 5.60; N, 14.95.

Reduction of 3-Bromo-4-nitroquinoline 1-Oxide (XI)——i) Catalytic Reduction: A solution of 300 mg of XI in 10 ml of EtOH was catalytically hydrogenated over 100 mg of 5% Pd–C. After absorption of 136 ml of H_2, the reaction was interrupted. After removal of the catalyst and the solvent, the resulting yellow residue was recrystallized from MeOH to give 110 mg of 4–aminoquinoline 1–oxide hydrobromide. Yield, 41%.

ii) With $NaBH_4$: To a suspension of 135 mg of XI in 5 ml of MeOH was slowly added 400 mg of $NaBH_4$ in N_2 atmosphere at 25°. After the reaction mixture was stirred at this temperature for 1 hr, the resulting yellow precipitates were collected on a filter, washed with H_2O and then dried. This was almost pure debrominated 4–hydroxyaminoquinoline 1–oxide (II). Yield, 31%.

iii) With Phenylhydrazine: A mixture of 200 mg of XI, 1 ml of EtOH, and 1 ml of phenylhydrazine was warmed at 60° for 1 hr. The yellow precipitates formed was collected and washed with ether. This yellow powder was almost pure 4–hydroxyaminoquinoline 1–oxide (II). Yield, 27%.

Reduction of 8-Methyl-4-nitroquinoline 1-Oxide (XIII)[17]——i) Catalytic Reduction: A solution of 250 mg of XII in 10 ml of EtOH was hydrogenated over 5% Pd–C at room temperature until absorption of hydrogen became slow, 3 moles of hydrogen, being consumed. After the resulting yellow precipitate was dissolved in the solution by the addition of 1 ml of conc. HCl, the catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from conc. HCl–MeOH to give 206 mg of 8–methyl–4–hydroxyaminoquinoline (XVII) hydrochloride as white needles. mp 275°. Yield, 80%. *Anal.* Calcd. for $C_{10}H_{11}ON_2Cl$: C, 56.96; H, 5.22; N, 13.29. Found: C, 57.03; H, 5.24; N, 12.93.

ii) With $NaBH_4$: To a suspension of 200 mg of XII in 10 ml of EtOH–H_2O (1:4 v/v%), 2.0 g of $NaBH_4$ was slowly added at 10° in N_2 atmosphere. After the reaction mixture was kept standing at room temperature for 5 days, the resulting white yellow precipitate was collected on a filter, washed with H_2O, and purified by Al_2O_3 column chromatography. From the $CHCl_3$ eluate, trace amounts of 8–methyl–4–nitroquinoline and the starting material were obtained. From the 5% MeOH–$CHCl_3$ eluate, XVII was obtained and recrystallized from conc. HCl–MeOH to give 80 mg of the hydrochloride of XVII. Yield, 39%.

Reduction of 8-Methyl-4-nitroquinoline (XIV) with $NaBH_4$——One gram of $NaBH_4$ was slowly added to a suspension of 100 mg of 8–methyl–4–nitroquinoline (XIV) in 5 ml of EtOH–H_2O (1:4 v/v%) in N_2 atmosphere at 23°. After stirring for 24 hr, the resulting yellow precipitate was filtered, washed with H_2O, and dried. This was 78 mg of pure 8–methyl–4–hydroxyaminoquinoline (XVII). mp 128°. Yield, 84%. Recrystallization from conc. HCl–MeOH gave the hydrochloride as white needles. mp 274—275° (decomp.).

Reduction of 8-Methyl-4-hydroxyaminoquinoline 1-Oxide (XVI) with $NaBH_4$——To a suspension of 40 mg of XVI, prepared by the phenylhydrazine–reduction of the corresponding nitro derivative,[8] in 5 ml of EtOH–H_2O (1:4 v/v%) in N_2 atmosphere, 400 mg of $NaBH_4$ was slowly added at 10° and the reaction mixture was stirred for 24 hr at 27° in N_2 atmosphere. The resulting white–yellow precipitates were collected on a filter, washed with water, and dried to 29 mg of pale yellow powder. This was identified as XVII. Yield, 80%.

8-Fluoroquinoline 1-Oxide——To a solution of 50 g of 8–fluoroquinoline, prepared from *o*–aminofluorobenzene, dissolved in 150 ml of AcOH, 50 ml of 30% H_2O_2 was added. After the reaction mixture was warmed at 65° for 6 hr, it was treated in usual manner for the preparation of N–oxides of quinoline derivatives. Six grams of 8–fluoroquinoline 1–oxide was obtained by recrystallization from acetone. Yield, 11%. mp 132°.

Nitration of 8-Fluoroquinoline 1-Oxide——A solution of 1.0 g of 8–fluoroquinoline 1–oxide dissolved in 15 ml of 79% H_2SO_4 was warmed at 90° and 0.8 g of KNO_3 was added in small portions. After the reaction mixture was kept at this temperature for 3 hr, it was poured on ice and extracted with $CHCl_3$. The extract was chromatographed over an Al_2O_3 column and eluted with benzene. From the earlier fractions, 180 mg of XV was obtained as pale yellow needles, mp 106°, by recrystallization from MeOH. Yield, 15%. *Anal.* Calcd. for $C_9H_5O_2N_2F$: C, 56.21; H, 2.60; N, 14.57. Found: C, 56.20; H, 2.57; N, 14.49.

From the later fractions 355 mg of 8–fluoro–4–nitroquinoline 1–oxide (XIII) was obtained as yellow needles, mp 160°, by recrystallization from MeOH. Yield, 28%. *Anal.* Calcd. for $C_9H_5O_3N_2F$: C, 51.89; H, 2.40; N, 13.45. Found: C, 52.19; H, 2.23; N, 13.30.

Catalytic Reduction of 8-Fluoro-4-nitroquinoline 1-Oxide (XIII)——A solution of 224 mg of XIII in 10 ml of EtOH was hydrogenated over 20 mg of 5% Pd–C at room temperature until absorption of hydrogen became very slowly. After 0.5 ml of conc. HCl was added the catalyst and solvent were removed by filtration and evaporation *in vacuo*, respectively. The residue was recrystallized from conc. HCl–MeOH to afford

16) Further purification was accompanied with decomposition.
17) The reduction by phenylhydrazine was already reported in the preceding paper.[8]

195 mg of 8–fluoro–4–hydroxyaminoquinoline (XVIII) hydrochloride as white needles, mp 281°, which was identical with the product from $NaBH_4$–reduction of XV. Yield, 84%. *Anal.* Calcd. for $C_9H_8ON_2FCl$: C, 50.32; H, 3.73; N, 13.05. Found: C, 50.52; H, 3.63; N, 13.08.

Reduction of 8-Fluoro-4-nitroquinloine (XV) with $NaBH_4$——To a suspension of 200 mg of XV in 5 ml of EtOH–H_2O (1:4 v/v%) was added 2.0 g of $NaBH_4$ at 10° in N_2 atmosphere with stirring. The resulting yellow precipitate were collected after 5 days and washed with H_2O. This was 140 mg of almost pure XVIII. mp 126°.

Reduction of 5-Nitroquinoline 1-Oxide——i) Catalytic Reduction: An EtOH solution of 200 mg of 5–nitroquinoline 1–oxide (XIX) was hydrogenated catalytically over 100 mg of 5% Pd–C. After absorption of 2 moles of H_2, the reaction was interrupted. After removal of the catalyst and the solvent, the resulting yellow residue was recrystallized from MeOH to yellow needles which was identified with 5–hydroxyamino-quinoline 1–oxide (XX) obtained by the $NaBH_4$–reduction described below. Yield, 33%.

ii) With $NaBH_4$: To a suspension of 200 mg of XIX in 5 ml of EtOH–H_2O (1:4 v/v%) was added 2.0 g of $NaBH_4$ in N_2 atmosphere at 5°. The reaction mixture was kept standing at 10° for 8 hr with stirring and the resulting yellow precipitate was collected on a filter, washed with H_2O, and recrystallized from MeOH. XX was obtained in 63% yield (149 mg), mp 190 °(decomp.). *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.78; H, 4.51; N, 15.54.

iii) With Phenylhyrazine: After a mixture of 200 mg of XIX, 1 ml of phenylhydrazine, and 4 ml of EtOH was warmed at 60° for 5 hr, excess of ether was added. The resulting precipitate was collected on a filter, washed with ether, and recrystallized from MeOH. XX was obtained in 39% yield.

Polarography——The polarograms were obtained by a Yanagimoto PA–102 Polarograph with an ordinary dropping mercury electrode at 25°. The solutions were adjusted to the pH of 4.00, 7.06, or 8.62 with buffers of acetic acid–acetate (M/10), K–Na–phosphates (M/15), and glycine–NaOH (M/10), respectively. Each half–wave reduction potential ($-E_{1/2}$) was calibrated against the saturated calomel electrode. The dissolved oxygen was removed by bubbling N_2 gas through the solution for about 10 min.

Acknowledgement The authors are greatly indebted to Dr. Waro Nakahara, Director of this Institute, for his hearty encouragement and useful discussion. Thanks are also due to Professor Keizo Tada of Kyoritsu Women's College of Pharmacy for his valuable discussion on the analyses of the polarograms. The financial suport from the Ministry of Education for a part of this work is gratefully acknowledged.