Examination of Reaction Condition——Reaction conditions varying reaction temperature, reaction period, reagent, solvent, addition procedure of reagent, pH of reaction mixture, addition of heavy metal ion etc., were examined. General procedure was as follows : Reducing reagent was added to a magnetically stirred mixture, 0.5 g. of 14-bromocodeinone (I) or 14-bromocodeine (II) and 5 ml. of solvent, in a 20 ml. flask. After completing a reaction, the organic solvent was distilled off *in vacuo* and then the residue extracted with $CHCl_3$. $CHCl_3$ extract was used as a sample for qualitative determination, comparing p.p.c. pattern of the extract with that of a standard sample from the reaction mixture obtained under Conroy's conditions.[1)] Experimental data was tabulated below. The pH of the reaction mixture was hardly maintained constant since pH increases as aq. $NaBH_4$ solution is added. The pH values at first and last point were described. Glass electrode pH meter, manufactured by Toa Denpa Kogyo, and Kolthoff buffer solution was utilized in these experiments.

The authors are indebted to Dr. Y. Kawazoe, National Cancer Center, for the measurement of NMR spectra and his kind discussion. They are also grateful to Mr. J. Nakahira, Sankyo Co., Ltd., for the supply of (−)-thebaine and to Misses H. Yamanouchi and K. Tohata, Institute of Applied Microbiology, University of Tokyo, for microanalyses and IR spectra.

Summary

Neopine (III), isoneopine (XXII) and indolinocodeine (XVII) were isolated from the sodium borohydride reduction mixture of 14-bromocodeinone (I) or 14-bromocodeine (II). The structures of new compounds, XVII and XXII, were elucidated. Hydroindole structure is comprised in XVII instead of hydroisoquinoline skeleton in codeine. The reaction mechanisms for production of the above three compounds were also discussed.

(Received February 3, 1965)

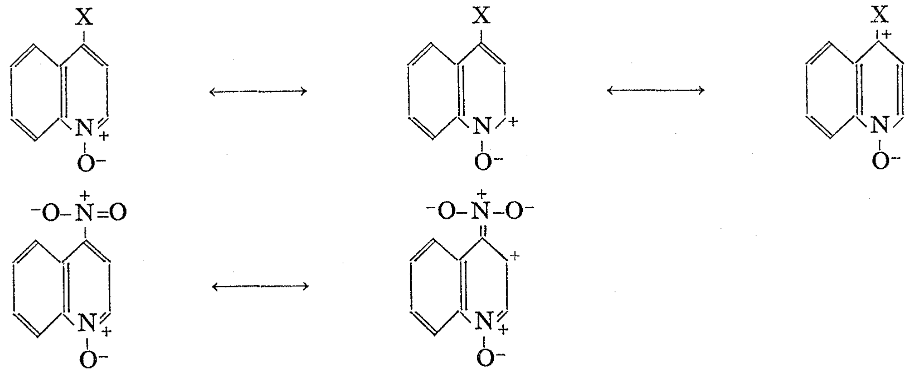
[Chem. Pharm. Bull. 13(9)1103~1107(1965)]

UDC 615.771.7 : 547.831.1.07

144. **Yutaka Kawazoe and Misako Tachibana** : Studies on Chemical Carcinogens. I. Reduction of 4-Substituted Quinoline N-Oxides with Sodium Borohydride.[*1]

(*National Cancer Center Research Institute*[*2])

It is well known that quinoline N-oxides substituted by an electron withdrawing group at 4 position (*i.e.*, nitro, halogeno, methylsulfonyl) are very reactive toward nucleophilic reagents. In case where the substituent is nitro group, nitro nitrogen and 3-carbon may also be reactive to nucleophiles. This may be illustrated by resonance canonical formulae as follows :



[*1] This paper also constitutes Part II of a series entitled "Studies on Hydrogen Exchange." Part I : This Bulletin, **11**, 1384 (1964).

[*2] Tsukiji, Chuo-ku, Tokyo (川添 豊, 橘 美佐子).

It is expected, therefore, that all of the skeletal atoms of pyridine moiety tend to be easily suffered from nucleophilic attack. As a matter of fact, there have been already known many reactions which are included in this category of reaction. Thus, for example, 4-nitroquinoline N-oxide undergoes replacement reactions with aqueous hydrogen halogenides to give 4-halogeno derivatives, which react further with nucleophiles such as amines, alkoxyl anions, etc. to give 4-replaced products.[1] It is recently reported by Richter and Rustad that a nucleophilic attack of sodiomalonate occurred at 3 position of 4-nitroquinoline N-oxide to give 3-substituted 4-nitroquinoline N-oxide.[2] Further, high reactivity of 2 position of N-oxides can be exemplified by deuterium exchange reaction with active deuterium of solvent molecules in presence of alkali.[3]

Now, this paper concerns the reaction of such molecules as having many cationic centers in one molecule with hydride anion which is one of the simplest nucleophilic reagent, 4-substituted quinoline N-oxides and sodium borohydride being used as the reactants. The reduction mechanism of sodium borohydride may be considered as initiated by attack of a hydride anion, which reacts with various cationic centers such as quaternary azomethins $>N^{+}=C<$ to give dihydroproducts $>N-CH<$, and carbonyl functions $>C=O$ to give alcohols $>CH-OH$ and also nucleophilic reactive centers of aromatic nuclei to result in a reductive replacement of the substituent attached.

When 4-nitroquinoline N-oxide was treated with a large excess of sodium borohydride in ethanol solution at room temperature, products I to V were isolated as shown in Chart 1.

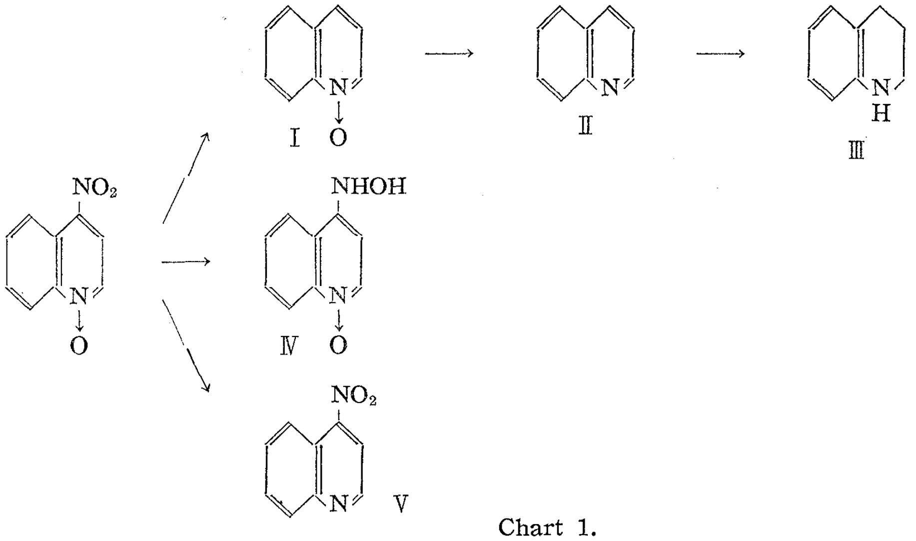


Chart 1.

It is interesting that a nucleophilic replacement occurred at 4 position with a hydride anion to give denitrated quinoline N-oxide. It has been known as an analogous reaction to the present case that nitro derivatives of 1,3,5-trichlorobenzene underwent a reductive replacement by the same reagent to produce denitro compounds prior to ring reduction. It seems to be closely related to the resonance contribution of a nitro group to aromatic nucleus, as suggested by Kaplan,[4] that which pathway may precede to others among ring reduction,[5] nucleophilic reductive replacement[4] or simple reduction

---

1) E. Ochiai: J. Org. Chem., **18**, 538 (1953); T. Okamoto, H. Hayatsu, Y. Baba: This Bulletin, **8**, 892 (1960); T. Okamoto, M. Itoh: *Ibid.*, **11**, 785 (1963).
2) H. J. Richter, M. E. Rustad: J. Org. Chem., **29**, 3381 (1964).
3) Y. Kawazoe, M. Ohnishi, Y. Yoshioka: This Bulletin, **12**, 1384 (1964). And our unpublished data.
4) L. A. Kaplan: J. Am. Chem. Soc., **86**, 740 (1964).
5) T. Severin, R. Schmitz: Chem. Ber., **95**, 1417 (1962); T. Severin, M. Adam: *Ibid.*, **96**, 448 (1963).

of nitro group.[6] It is of interest in this connection that 4-nitro group was reduced to hydroxylamine in about 25% yield in the present case, although nitrobenzene and 1-nitronaphthalene are almost inert under this reaction condition. Further reduction of 4-hydroxylaminoquinoline N-oxide thus produced may be prevented because of its precipitation out of the reaction mixture due to its very poor solubility.

Then, quinoline N-oxide and its 4-chloro derivative were reduced under the same condition, the results being shown in Chart 2.

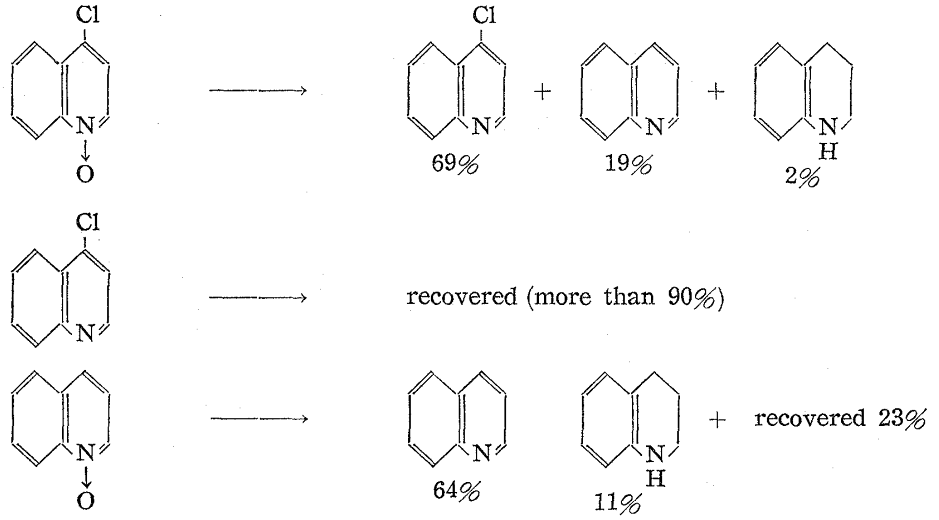


Chart 2.

4-Chloroquinoline N-oxide seems to have been reduced in two different ways as expected. Thus, one was deoxygenation of N-oxide group and the other was nucleophilic reductive replacement of 4-chloro group, followed by deoxygenation to give free quinoline. This was supported by the fact that 4-chloroquinoline was almost recovered under the same reaction condition and that, therefore, quinoline yielded in 20% from 4-chloro N-oxide can be considered as produced *via* quinoline N-oxide derived by reductive replacement of 4-chloroquinoline N-oxide.

Now, next point to interest us was the mechanism of deoxygenation of N-oxide group. Two mechanisms may be realized, which are illustrated in Chart 3.

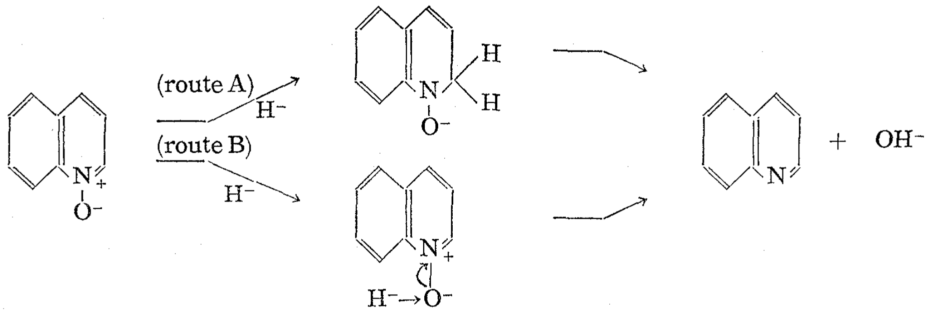


Chart 3.

Thus, one is started with hydrogenation of azomethin group, followed by dehydroxylation. The other is direct oxygen-transfer to hydride anion. In the present case, deoxygenation may be considered to go through dihydro compound as the reaction scheme A, which is true for the reduction of quaternary halogenides of pyridine and quinoline

---

[6] C.E. Weill, G.S. Panson: J. Org. Chem., **21**, 803 (1956).

homologues.[7] In order to prove it, 2-deuteroquinoline N-oxide was reduced and the loss of deuterium at 2 position of the reduced quinoline was examined by nuclear magnetic resonance spectroscopy. Thus, more than 15% of deuterium was found to be lost, replaced by light hydrogen. It may, therefore, be concluded with consideration of the isotope effect in dehydration process that deoxygenation was initiated by the hydride attack to 2 position, followed by dehydration of dihydro compound as an intermediate.[*3] It could be finally confirmed by the reduction of non-labeled quinoline N-oxide by sodium borodeuteride in deuteroethanol, which is now being pursued in our laboratory.

It was revealed as a conclusion that 4-nitroquinoline N-oxide underwent competitive nucleophilic reactions by hydride anion at various reactive center in its molecule as described in the first part of this paper, that is, at nitro nitrogen, 4-carbon and 2-carbon, at least.

It is noteworthy, furthermore, to note that when the reaction medium was changed from ethanol to methanol, a serious change was observed in reduction of 4-nitroquinoline N-oxide. Thus, no quinoline N-oxide could be detected even by thin-layer chromatography and the yield of 4-hydroxylaminoquinoline N-oxide was raised up to 40%, so that this reaction can be used for preparation of 4-hydroxylaminoquinoline N-oxide in a simple procedure.[8]

As borohydride reduction seems, in general, to be strongly dependent on solvent and other reaction conditions, the reaction with N-oxides is still open to further investigation for complete understanding.

Experimental

Reduction of Quinoline N-Oxide with Sodium Borohydride——i) In ethanol: 0.828 mg. of anhydrous 2-deuterated quinoline N-oxide dissolved in 10 ml. of ethanol was added to an ethanolic solution of 1.36 g. of $NaBH_4$ with stirring. After the reaction mixture was kept standing at room temperature for 5 hr., it was acidified by dropwise addition of diluted aqueous acetic acid, followed by evaporation of ethanol under reduced pressure. The aqueous residue was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was chromatographed eluted with benzene and then $CHCl_3$, fractionated as follows: 88 mg. of tetrahydroquinoline, 495 mg. of deoxygenated quinoline and then 220 mg. of recovered quinoline N-oxide in this order. The yields are 11%, 64% and 23%, respectively.

ii) In tetrahydrofuran: When tetrahydrofuran took place of ethanol as reacting solvent, 870 mg. of quinoline N-oxide gave 426 mg. of quinoline (55%), 163 mg. (19%) of recovered quinoline and 61 mg. (8%) of tetrahydroquinoline under the reaction condition described in (i).

Reduction of 4-Chloroquinoline N-Oxide——i) In ethanol: 718 mg. of 4-chloroquinoline N-oxide dissolved in 10 ml. of ethanol was added to an ethanolic solution containing 907 mg. (6 mol. equivalent to the oxide) of $NaBH_4$. After the reaction mixture was kept standing at room temperature for 5 hr., it was acidified by addition of diluted aqueous acetic acid, concentrated up to a small volume of the solution and then extracted with $CHCl_3$. By chromatographic separation were obtained 450 mg. of deoxygenated 4-chloroquinoline (69%), 12 mg. of recovered 4-chloroquinoline N-oxide (2%) and 100 mg. of free quinoline (19%).

ii) In tetrahydrofuran: When tetrahydrofuran was used as the solvent instead of ethanol, 539 mg. of deoxygenated 4-chloroquinoline (71%) and 71 mg. of recovered 4-chloroquinoline N-oxide (13%) were obtained. No quinoline nor its N-oxide was detected even on thin-layer chromatography.

Reduction of 4-Chloroquinoline with Sodium Borohydride——539 mg. of 4-chloroquinoline was reduced with 680 mg. of $NaBH_4$ under the same condition as described for 4-chloroquinoline N-oxide. More than 90% of the starting material was recovered and quinoline and tetrahydroquinoline were obtained in so poor yield as to be only detectable.

[*3] No hydrogen exchange was confirmed to occur at all for 2-hydrogens of either quinoline or its N-oxide under this reaction condition, as far as deoxygenation process was not included.

7) R. E. Lyle, D. A. Nelson, P. S. Anderson: Tetrahedron Letters, **1962**, 553; P. S. Anderson, R. E. Lyle: *Ibid.*, **1964**, 153.

8) M. Tachibana, Y. Kawazoe, K. Aoki, W. Nakahara: Gann, **56**, 85 (1965).

Reduction of Quinoline with Sodium Borohydride——387 mg. of quinoline was treated with 680 mg. of $NaBH_4$ in 20 ml. of ethanol for 5 hr. Products were extracted and purified as described above. 50% of tetrahydroquinoline was obtained and the rest of them was the starting material recovered.

Reduction of 4-Nitroquinoline N-Oxide with Sodium Borohydride——i) In ethanol: 760 mg. of 4-nitroquinoline N-oxide dissolved in 10 ml. of ethanol solution of 756 mg. of $NaBH_4$ in N_2 atmosphere under ice-cooling. After 3 hr.'s stirring of the reaction mixture, it was concentrated to a half volume under reduced pressure, when crystalline precipitates came out. Then, they were gathered and washed with methanol, which was 188 mg. of almost pure 4-hydroxylaminoquinoline N-oxide (25%). The mother liquid and the washings were combined and acidified with 10% aqueous acetic acid and then, neutralized with $NaHCO_3$, followed by extraction with $CHCl_3$. The extract was purified chromatographically to give 15 mg. of 4-nitroquinoline (2.2% yield), 52 mg. of quinoline N-oxide (9%), small amounts of quinoline and tetrahydroquinoline and, moreover, a considerable amount of colored material which showed many spots on thin-layer chromatography.

ii) In methanol: 2 g. of 4-nitroquinoline N-oxide dissolved in 30 ml. MeOH was slowly added to a solution of 4 g. of $NaBH_4$ in 30 ml. MeOH in a period of 40 min. The reaction mixture was maintained at 0° to 5° during addition and then, kept standing at room temperature for 1 hr., when crystalline precipitates were come out. They were 250 mg. of almost pure 4-hydroxylaminoquinoline N-oxide. The filtrate was acidified with diluted aqueous HCl and concentrated to a small volume under reduced pressure. It was, then, made alkaline with $NaHCO_3$, when precipitates of 4-hydroxylaminoquinoline N-oxide came out again (500 mg.). The mother liquid was extracted with a large amount of $CHCl_3$. When $CHCl_3$ layer was dried and concentrated to a small volume, orange crystal came out. It was found to be 180 mg. of 4,4′-azoxyquinoline N,N′-dioxide.[9]

The authors are gratefully indebted to Dr. Waro Nakahara, Director of this institute, for his interest and encouragement throughout this work.

Summary

4-Substituted quinoline N-oxides were reduced by sodium borohydride and the reaction mechanism was discussed. It was revealed, for example, that 4-nitroquinoline N-oxide underwent competitive nucleophilic reactions to produced denitrated quinoline N-oxide, deoxygenated 4-nitroquinoline and 4-hydroxylaminoquinoline N-oxide which is a reduction product of nitro group, respectively.

(Received February 12, 1965)

---

[9] E. Ochiai, A. Ohta, H. Nomura: This Bulletin, 5, 310 (1957).