# CONTRIBUTIONS OF PROFESSOR MASATOMO HAMANA IN HETEROCYCLIC CHEMISTRY

—Research Life of a Scientist in Heteroaromatic *N*-Oxide Chemistry—

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It is my great pleasure and privilege to introduce scientific contributions by Professor Masatomo Hamana in this special issue of Heterocycles as one of juniors in the same field. One of the factors which define the greatness of a scientist will be his attitude for his main research subject. Prof. Hamana has carried out his original intention in organic chemistry with his constant interest and firm consideration to the chemical behavior of heteroaromatic *N*-oxides. Thus he seems to be born under the research of heterocyclic chemistry. Before introducing his scientific contribution, the author would like to describe the background of his investigation briefly.

During the 2nd World War, a systematic investigation of heteroaromatic *N*-oxides by late Prof. E. Ochiai developed independently of foreign chemists. The results obtained in this period by Japanese chemists under supervision of Prof. Ochiai gave a big impact to heteroaromatic chemistry, when the results were opened after the War.[1] The early investigation in Japan was concentrated on the chemistry of pyridine and quinoline *N*-oxides, but since around 1960, the research has been gradually extended to diazines, benzodiazines, and some of azoles by many groups, because the behavior of *N*-oxides observed on monoazine series seems to be quite fresh and fascinating to many chemists suggesting a new method for the synthesis of various heteroaromatic compounds.

According to a viewpoint of the author, the early investigations of monoazine *N*-oxides are divided into two major stages.

1) Just after discovery of the selective formation of 4-nitropyridine *N*-oxide by nitration of pyridine *N*-oxide in 1942,[2] the synthesis of pyridine and quinoline derivatives starting from the nitration of these monoazine *N*-oxides and involving subsequent replacement of the active 4-nitro groups was a major subject during the first stage of the investigation.

2) In the second stage of the investigation, the nucleophilic addition-elimination reaction of monoazine *N*-oxides became apparent to have wide applicability to the synthesis of various derivatives of monoazine series. When these stages of the investigation were nearly finished, diazine and benzodiazine *N*-oxides were subsequently incorporated into the research field as substrates, and the method employed in monoazine *N*-oxide chemistry has been recognized to be versatile for the synthesis of diazine derivatives with many successful results.

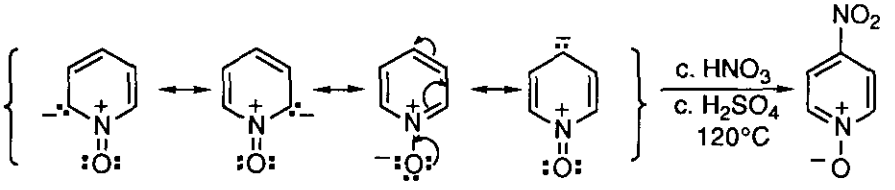
Prof. Hamana, as a propulsive co-worker of Prof. Ochiai, first gave a big contribution by his fine work on the removal of *N*-oxide function which sometimes remained on the synthesized compounds as an obstinately resistant group to deoxygenation. This work can be evaluated to be a finishing blow in the last part of stage 1.

In the stage 2, he made comprehensive works on carbon-carbon bond formation on heteroaromatic rings, using mainly reactions of quinoline *N*-oxides with carbon nucleophiles under various conditions. It should be mentioned that other than these subjects he has much interest on the mechanism of *N*-oxide reactions, so that he showed many interesting findings connecting settlements of undissolved questions of *N*-oxide chemistry.

Then, the author outlines his great footmarks in this field concretely.

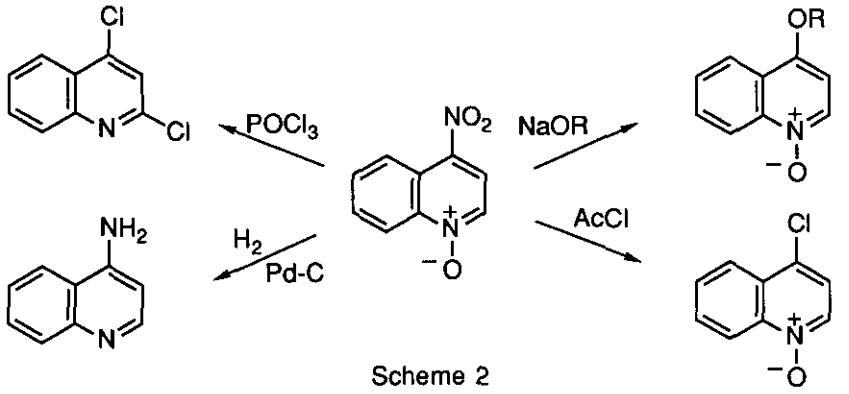
**A) Removal of *N*-Oxide Function with Phosphorus Trihalides**

As reported independently by Prof. Ochiai and Prof. den Hertog, the nitration of pyridine *N*-oxide and quinoline *N*-oxide gave the corresponding 4-nitro derivatives due to the electron-donating effect of the *N*-oxide function pointed out by Linton in 1940.[3]




Scheme 1

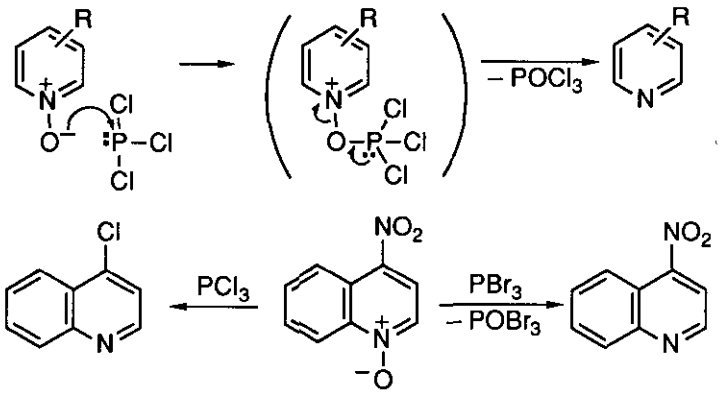
The 4-nitro derivatives thus obtained are useful intermediates for the synthesis of 4-substituted pyridines and quinolines as exemplified by 4-nitroquinoline *N*-oxide in Scheme 2.




Scheme 2

In some cases, the *N*-oxide group is still remain after converting the 4-nitro group into other substituents. Accordingly, it was naturally desired to find a versatile method for removing the *N*-oxide group from the reaction products other than catalytic reduction without influence on co-existing substituents. Prof. Hamana, at the early stage of his research life, fixed his attention to the affinity of trivalent phosphorus compounds to oxygen atom and examined the reaction of pyridine and quinoline *N*-oxides with phosphorus trichloride and tribromide.[4] The reaction proceeded as expected, and the original tertiary amines were isolated with phosphoryl halide being formed. The reaction has wide applicability and experimental simplicity, and until now, it is used habitually in laboratory scale synthesis.

It should be emphasized that the reagents have selective affinity to *N*-oxide functions. For example, 4-nitropyridine *N*-oxide reacted with phosphorus trichloride to give 4-nitropyridine. In the case of 4-nitroquinoline *N*-oxide, the reaction with phosphorus trichloride tends to give 4-chloroquinoline in place of 4-nitroquinoline, but the desired compounds (4-nitroquinoline) is satisfactory obtained by use of phosphorus tribromide (Scheme 3).



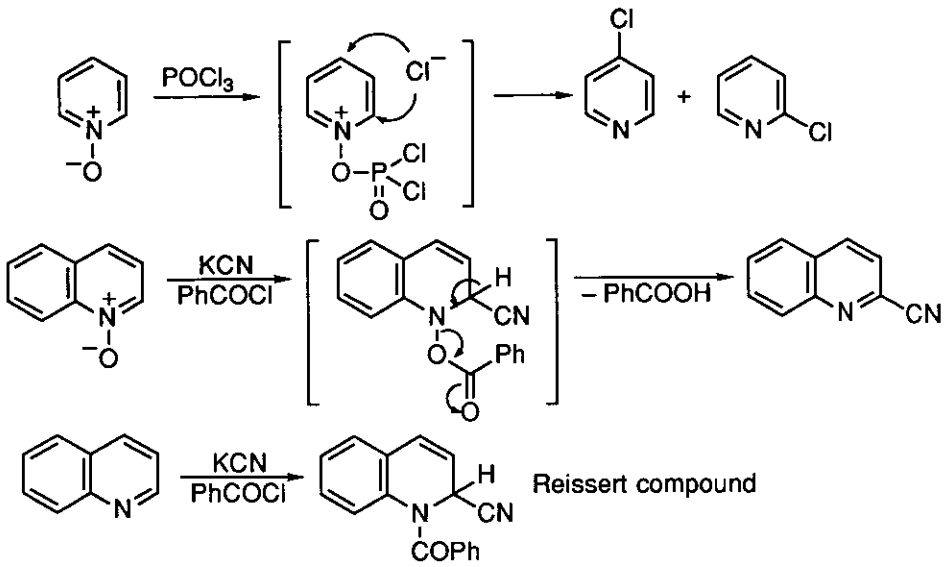

Scheme 3

At present, there are several methods for the removal of *N*-oxide groups by means of low valent inorganic reagents other than phosphorus trihalides, but Hamana's reduction can be evaluated to be the initiative of these methods.

**B) Nucleophilic Substitutions in the Presence of Acylating Agent**

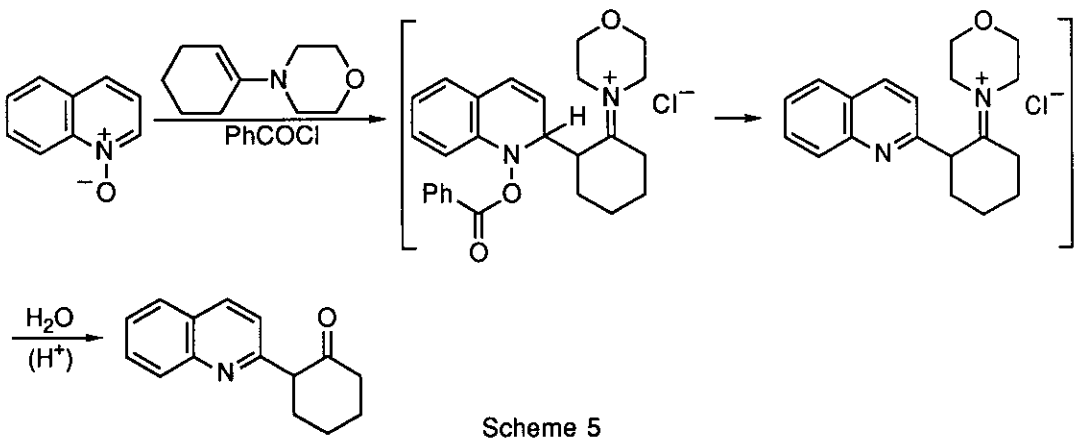
After the investigation described above, he changed his position from Tokyo University to Kyushu University and started a new project on the *N*-oxides which would become his life work.

In 1898, Bobranski reported that pyridine *N*-oxide reacted with phosphoryl chloride to give a mixture of 2-chloro- and 4-chloropyridines. Before two years, Henze treated quinoline *N*-oxide with potassium cyanide in the presence of benzoyl chloride and obtained 2-cyanoquinoline in excellent yield (Reissert-Henze reaction).[5] The common feature of these reactions is the initial acylation of the *N*-oxide function which strongly promotes subsequent attack of nucleophiles to heteroaromatic rings. Further, the intermediates of Reissert-Henze reaction, unlike Reissert compounds, have a structural advantage for aromatization.



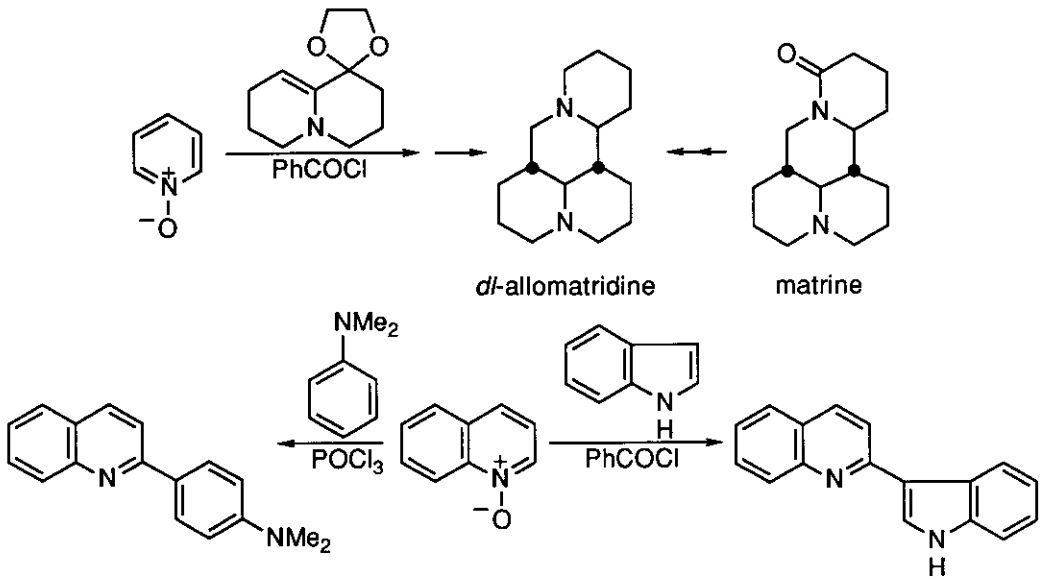

Scheme 4

Based on these consideration, Prof. Hamana surmised that an appropriate combination of an acylating agent with a carbanion or its equivalent species opens a new way to a carbon-carbon bond forming reaction of heteroaromatic rings. This assumption was proved to be adequate by reaction of quinoline *N*-oxide with cyclohexanone morpholine enamine in the presence of benzoyl chloride. The reaction gave 2-(2-oxocyclohexyl)quinoline, after subsequent hydrolysis of the unstable reaction intermediate.[6]



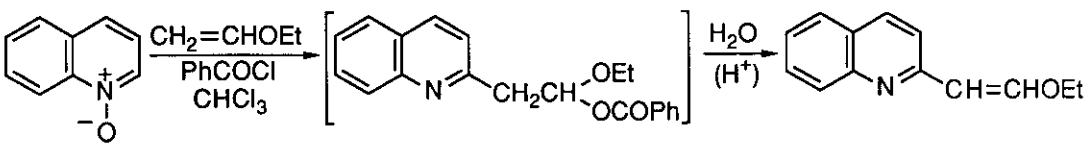

Scheme 5

According to this manner, in 1970 he succeeded in synthesis of *dl*-allomatridine derived from matrine, an alkaloid of *Sophora alopecuroides* L. Furthermore, π-electron-sufficient aromatics such as dimethylaniline and indole can be introduced directly into the 2-position of quinoline rings.



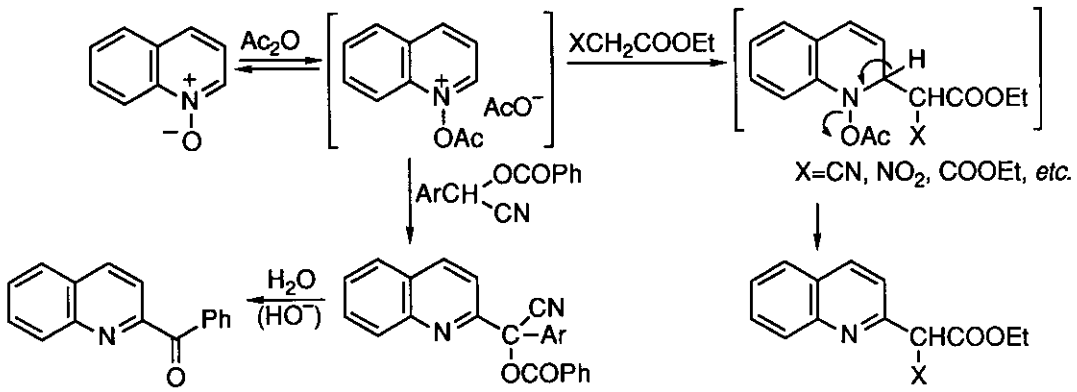

Scheme 6

As well as enamines, some enol ethers smoothly react with quinoline *N*-oxide to give the derivatives containing a functionalized carbon side-chain at the 2-position. In the case of the reaction with ethyl vinyl ether, an intermediate shown in the brackets was isolated at low reaction temperature, by his fine technique in experiments.




Scheme 7

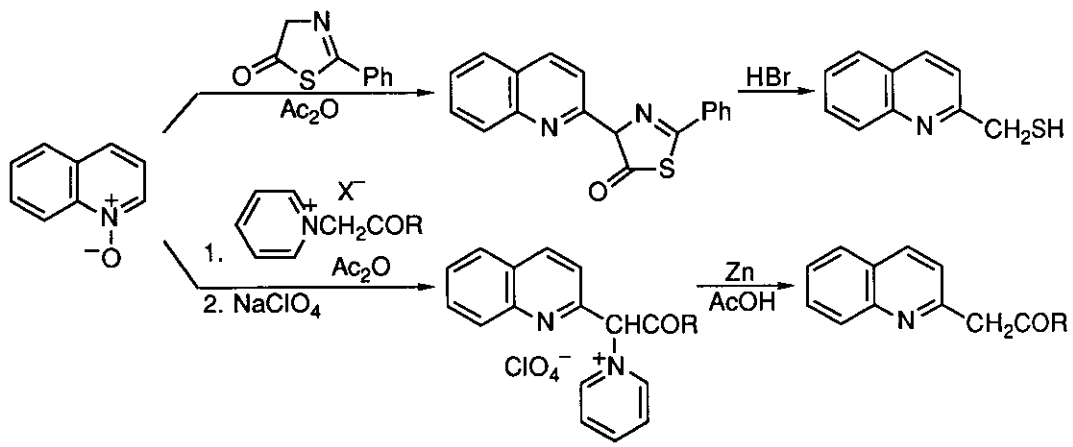
Active methylene compounds, such as ethyl cyanoacetate, diethyl malonate, ethyl nitroacetate, and so on, reacted with quinoline *N*-oxide according to the mechanism shown in Scheme 8. Benzoates of aryl aldehyde cyanohydrins are useful reagents for the introduction of aroyl groups into the 2-position of quinoline rings. In these substitution, acetic anhydride was observed to be a better promoter than benzoyl chloride.




Scheme 8

An extension of this substitution was made by using 2-phenyl-5-oxazolone and 2-phenyl-5-thiazolone as an active methylene compound. These azoles reacts smoothly with quinoline *N*-oxides under similar conditions to give the quinoline derivatives with the corresponding azole moiety at the 2-position. The subsequent hydrolysis of the azole moiety with acid yields the 2-(substituted methyl)quinolines.

Further, the reaction of quinoline *N*-oxides with 1-acylmethylpyridinium halides followed by reductive removal of the pyridinium moiety was developed as a versatile method for the synthesis of 2-acylmethylquinolines

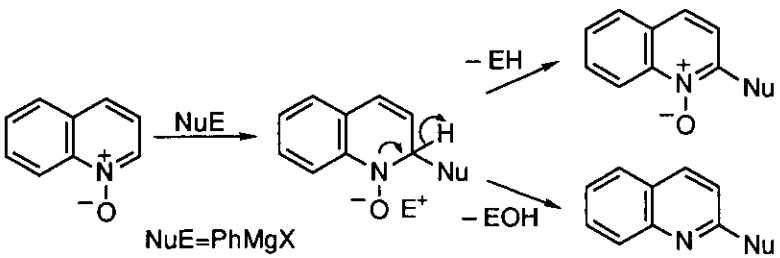



Scheme 9

The above reactions of a heteroaromatic *N*-oxide with a carbon nucleophile in the presence of an appropriate acylating reagent brought about fruitful results in the introduction of a carbon-substituent into a π-deficient nitrogen heteroaromatics. Now, the synthesis of monoazine, diazine, or benzodiazine derivatives with a functionalized carbon side-chain is sharing in the benefit from the above methods developed by Prof. Hamana and his co-workers.

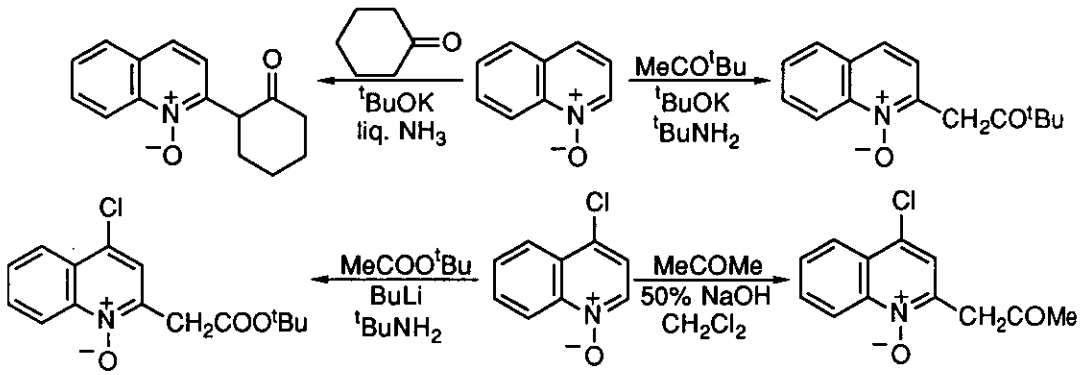
**C) Carbon-Carbon Bond Formation under Basic Conditions**

When quinoline *N*-oxide was treated with phenylmagnesium bromide under traditional conditions, 2-phenylquinoline *N*-oxide (major product) and 2-phenylquinoline (minor product) were obtained. The formation of the former suggested the presence of different type addition-elimination reaction of quinoline *N*-oxides from the reactions described in Section B, *i.e.* the elimination of hydride from the 2-position is the crucial step for aromatization, and the *N*-oxide group remains in the product.




Scheme 10

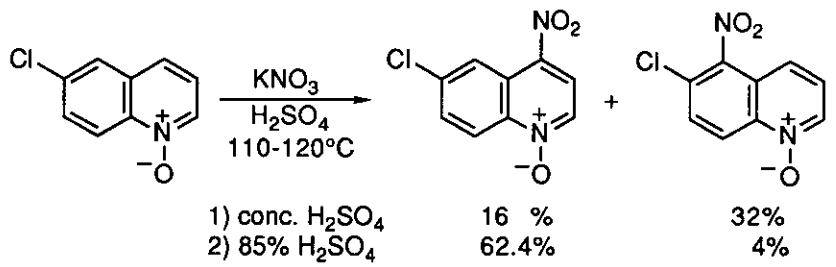
Considering the reaction mechanism shown in Scheme 10, Prof. Hamana investigated the reaction of quinoline *N*-oxide with active methylene compounds under a variety of strongly basic conditions and obtained 2-substituted quinoline *N*-oxides, as expected. In the case of 4-chloroquinoline *N*-oxide, the reaction takes place only at the 2-position, and surprisingly the replacement of the 4-chloro substituent is not detected at all. Thus, he established a novel nucleophilic displacement of the α-hydrogen with carbon-nucleophiles in the quinoline *N*-oxide series. Some typical examples are shown in Scheme 11.[7]




Scheme 11

**D) Investigation on the Reaction Mechanism of *N*-Oxides**

i) Electrophilic Substitution—In 1950, it was found that nitration of quinoline *N*-oxides is markedly temperature-dependent; that is, treatment of quinoline *N*-oxide with potassium nitrate in concentrated sulfuric acid at elevated temperature (70-120°C) gives exclusively 4-nitroquinoline *N*-oxide, but 5- and 8-nitro derivatives are formed in the reaction at low temperature (below 40°C). Prof. Hamana disclosed that the concentration of sulfuric acid is a more important factor influencing the direction of the nitration than the reaction temperature, and the use of the acid of somewhat lower concentration (*ca.* 80-85%) is generally favorable for the 4-nitration. Nitration of 6-chloroquinoline *N*-oxide is presented as an example in Scheme 12.

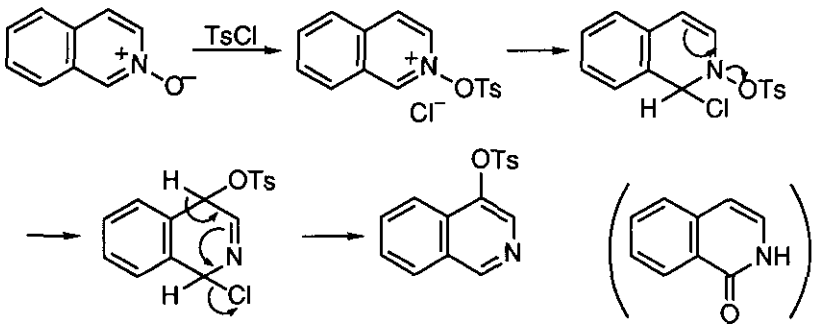



Scheme 12

Another question on the electrophilic substitution of pyridine and quinoline *N*-oxides was "Is there any reaction occurred at the 4-position other than the nitration ?" For example, the sulfonation of pyridine *N*-oxide gives rise to the 3-sulfonic derivative, and the bromination with bromine results into the formation of a complicated mixture. By using bromine with thallium triacetate as a bromi-

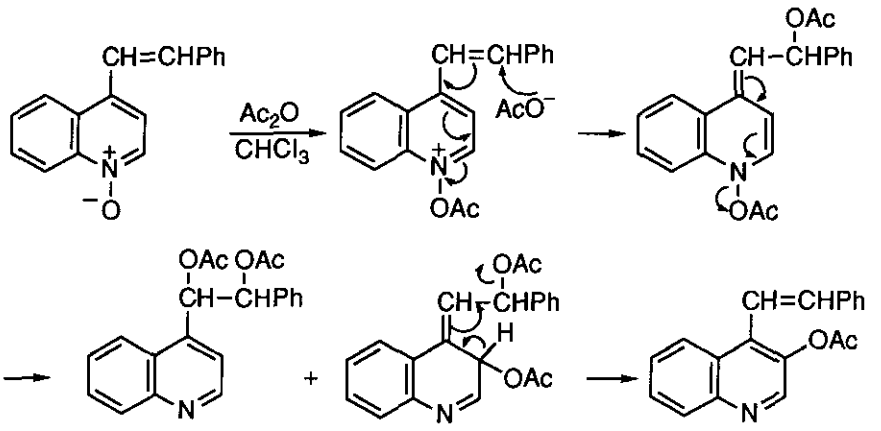
nating agent, Prof. Hamana obtained 4-bromoquinoline *N*-oxide and some 4-bromopyridine *N*-oxides.

ii) β-Substitution with Nucleophiles—With the growth of the *N*-oxide chemistry, the reactions which gave β-substituted products under nucleophilic conditions began to be observed. A typical example is the reaction of isoquinoline *N*-oxide with *p*-toluenesulfonyl chloride giving 4-(*p*-toluenesulfonyloxy)isoquinoline as the major product, which is rationalized by the mechanism illustrated in Scheme 13.[9]



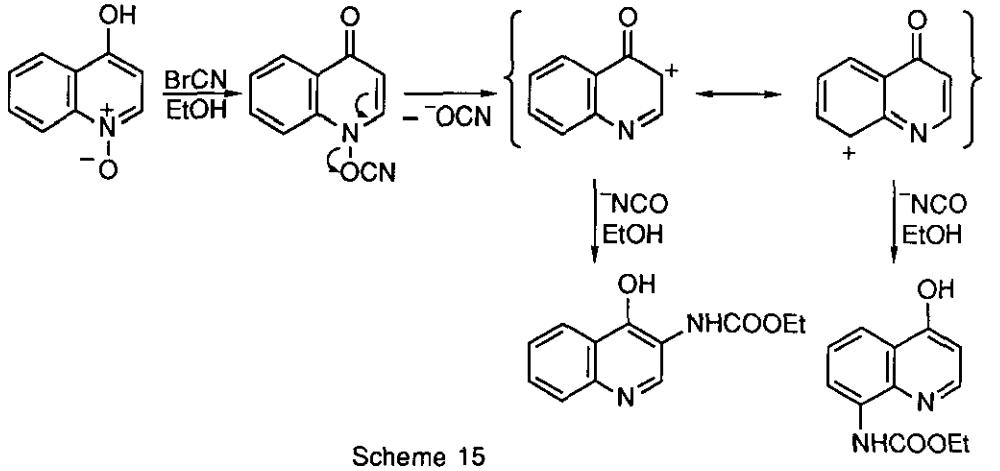

Scheme 13

Although the corresponding 3-substituted quinoline is not formed in the reaction of quinoline *N*-oxide itself, Prof. Hamana noticed the occurrence of this type of reaction in a series of quinoline *N*-oxides. For example, the reaction of 4-styrylquinoline *N*-oxide with acetic anhydride gave 4-(1,2-diacetoxy-2-phenylethyl)quinoline and 3-acetoxy-4-styrylquinoline. As shown in Scheme 14, the reaction can be explained by a multistep process which initiated by acetylation of the *N*-oxide group and involves the 1,4-dihydroquinoline as the key intermediate.



Scheme 14

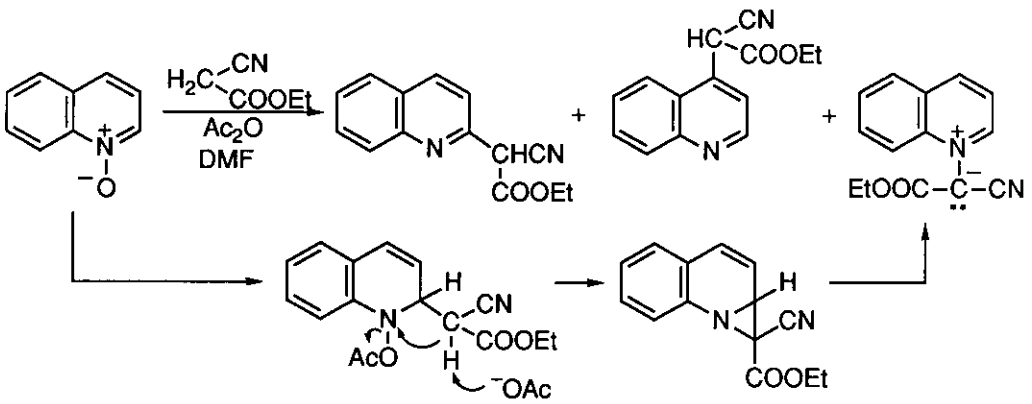
When 4-hydroxyquinoline *N*-oxide was treated with cyanogen bromide, 3-ethoxycarbonylamino-4-hydroxyquinoline was isolated as a major product. As shown in Scheme 15, formation of this compound can be understood by the similar mechanism to those described above. Thus, according to his fine work, the behavior of quinoline *N*-oxides and isoquinoline *N*-oxides for nucleophilic substitution became understandable in a unified form.



Scheme 15

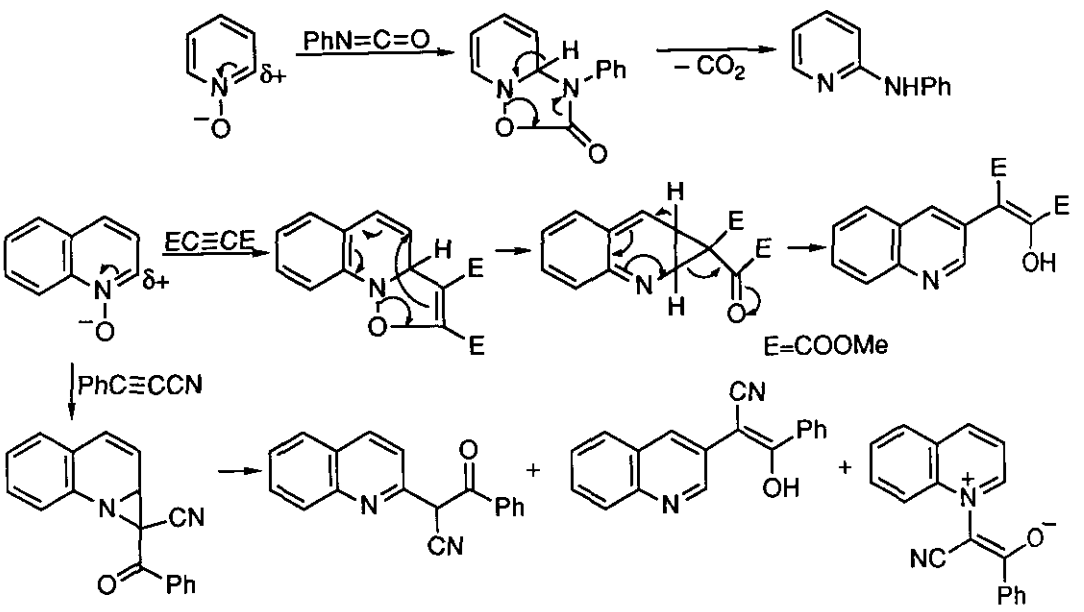
iii) Formation of Aziridine Intermediate—When the reaction of quinoline *N*-oxide with ethyl cyanoacetate and acetic anhydride was carried out in dimethylformamide, the result was different from that of the reaction illustrated in Scheme 8. In this case, the 1-substituted quinolinium betain was

obtained together with minor amounts of 2- and 4-substituted quinolines. Prof. Hamana explained the formation of the betain reasonably by assuming an aziridine intermediate. This is the first proposal of aziridine formation in *N*-oxide chemistry.



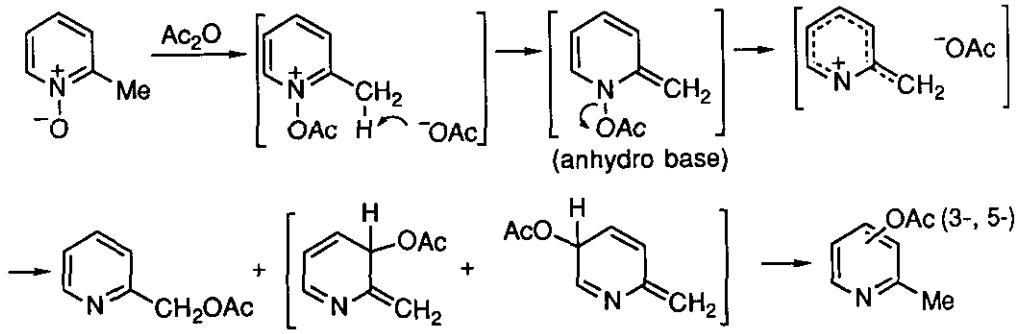

Scheme 16

Since his proposal, aziridine intermediates are conveniently adopted for explaining the formation of unusual products from the reactions of heteroaromatic *N*-oxides. One example is the formation of betains in 1,3-dipolar cycloaddition reactions of the *N*-oxides. The cycloaddition of pyridine *N*-oxide with phenyl isocyanate gave 2-anilinopyridine.[10] The reaction of this type was once accepted to be standard one, but with the progress of the research work on the cycloaddition reaction, a variety of the products began to be obtained depending on the nature of *N*-oxides and 1,3-dipolarophiles employed. Likely mechanism of the formation of products, in some cases, is shown reasonably by incorporating the existence of aziridine intermediates derived by sigmatropic rearrangement reactions.[11]



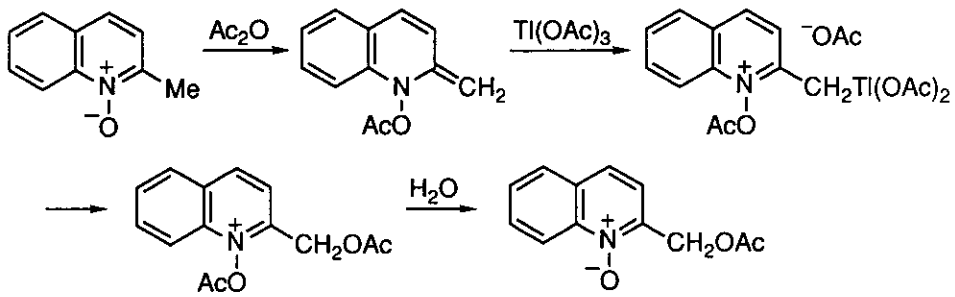

Scheme 17

iv) Side-Chain Acetoxylation—It is well known that the reaction of 2-methylpyridine *N*-oxide with acetic anhydride gives rise to a mixture of 2-acetoxymethylpyridine and 3-(and 5-)acetoxy-2-methylpyridines, and no formation of 6-methyl-2-pyridinone was observed. This reaction is generally accounted for by the path involving the *N*-acetoxypyridine anhydro base as the key intermediate, and apparently the extrusion of the acetoxyl group from the anhydro base promotes the above reaction (Scheme 18).[12]




Scheme 18

Prof. Hamana directed his attention to the reverse reactivity, an enamine-like one, of the anhydro base and explored its electrophilic reactions. Thus, he succeeded in realization of this type of reaction by treating 2-methylquinoline *N*-oxide with thallium triacetate in the presence of acetic anhydride to afford 2-acetoxymethylquinoline *N*-oxide. Similar result was obtained by use of lead tetraacetate in acetic anhydride (Scheme 19).




Scheme 19

As described in this paper, it would be not over-expression to say that the research life of Prof. Hamana was concentrated to the solution of the following question: "What is the nature of heteroaromatic *N*-oxide?" In addition to that, the present author would like to emphasize that nowadays he is one of the most earnest and trustworthy leaders of heteroaromatic chemists in Japan through his continuous encouragement to his junior researchers. In 1982, he retired from Kyushu University, but he is still an active chemist working in Chugai Pharmaceutical Co. Ltd. as a research consultant. In fact recently, he proposed a novel mechanism involving the 2-carbanion intermediate for the reaction of nicotinic acid *N*-oxide with acetic anhydride, and also reported some interesting observations on the vicarious nucleophilic substitution of quinoline *N*-oxide. In this occasion, the author hopes his prosperity and continuous achievement for many more years.

**ACKNOWLEDGEMENTS**

The author sincerely thanks Prof. Masatomo Hamana for his sending reprints of his recent papers to the author for preparing this articles. Thanks are also due to Prof. K. Fukumoto for his suggestion on writing this articles.

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