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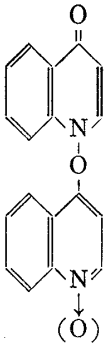
Formation of 3,3'-(4,4'-Dihydroxy)bipyridine Presentation of a Novel Homolytic Fission of N-O Bond

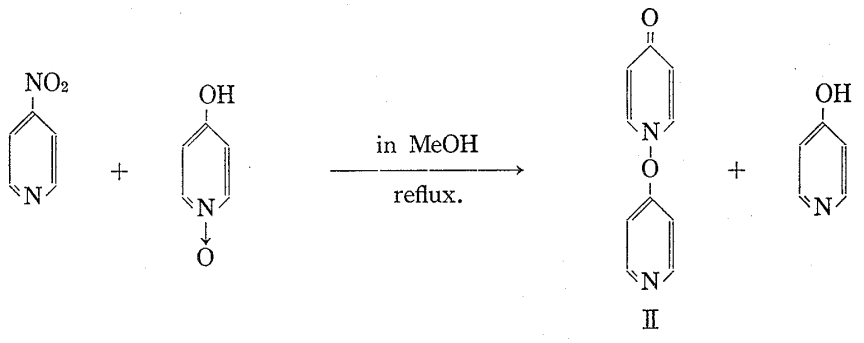
Previously,[1] it has been reported that 3,3'-(4,4'-dihydroxy)biquinoline was formed in the reaction of 4-nitroquinoline 1-oxide and 4-hydroxyquinoline 1-oxide, and the reaction mechanism has been postulated in a free radical way. But an important intermediate for elucidation of the reaction mechanism as illustrated as compound (I) has not yet been isolated in the reaction.



I

This paper deals with isolation of compound I type intermediate and further presentation of a novel homolytic fission of N–O bond.

A solution of 4-nitropyridine and 4-hydroxypyridine 1-oxide in methanol was refluxed for ten hours to give colorless plates (II), $C_{10}H_8O_2N_2$, mp 130° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 270.5 (4.27), IR ν_{max}^{KBr} cm^{-1} 1616 (carbonyl) in 76% yield, mass spectrum *m/e*: 188 (M^+), in addition to 4-hydroxypyridine (trace), and an evolution of nitrogen dioxide gas was observed. II gave a brown color with ferric chloride solution. Its nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) showed signals at 1.27 τ (2H doublet doublet, J=5 and 1.5 cps), 3.11 τ (2H doublet doublet, J=5 and 1.5 cps), 2.37 τ (2H doublet, J=9 cps) and 3.55 τ (2H doublet, J=9 cps). Based on the comparison with the NMR spectra of N-(4'-pyridyl)-4(1H)-pyridone[2] and N-methoxy-4(1H)-pyridone as shown in Table I, the signals at 2.37 τ and 3.55 τ were assigned as AB-type protons in N-alkyloxy-4(1H)-pyridone. From above results, it is reasonable to assume that II is N-(4'-pyridyloxy)-4(1H)-pyridone.[3]



II

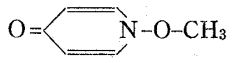
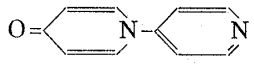
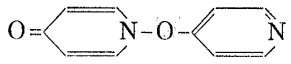
Chart 1

Treatment of II in benzene, toluene or dioxane at 100° produced white needles (III) $C_{10}H_8O_2N_2$, mass spectrum *m/e*: 188 (M^+), UV λ_{max}^{EtOH} mμ (log ε): 262 (4.19), IR ν_{max}^{KBr} cm^{-1} 1628 in 70—80%, in addition to 4-hydroxypyridine (trace).

Reaction of III with a mixture of phosphorus pentachloride and phosphorus oxychloride afforded colorless needles (IV), $C_{10}H_6N_2Cl_2$, mass spectrum *m/e*: 224 (M^+), mp 110°, UV λ_{max}^{EtOH} mμ (log ε): 262.5 (3.70) in 92% yield, whose NMR spectrum (CCl_4) showed signals at 1.38 τ (4H broad doublet, J=5.8 cps) and 2.50 τ (2H doublet, J=5.8 cps). Catalytic hydrogenation

1) T. Kosuge, H. Zenda, H. Sawanishi, and Y. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **17**, 2178 (1969).
2) M. Hamana and H. Yoshimura, *Yakugaku Zasshi*, **72**, 1051 (1952).
3) II was also obtained from the reaction of 4-hydroxypyridine 1-oxide with 4-chloropyridine. T. Kosuge, *et al.*, unpublished data.

Table I.

	Chemical shift τ (coupling const.)
	2.36 (doublet, J=8.2 cps) 3.69 (doublet, J=8.2 cps)
	2.28 (doublet, J=8.0 cps) 3.44 (doublet, J=8.0 cps) 1.18 (doublet doublet, J=5 and 1.5 cps) 2.64 (doublet doublet, J=5 and 1.5 cps)
	2.37 (doublet, J=9 cps) 3.55 (doublet, J=9 cps) 1.27 (doublet doublet, J=5 and 1.5 cps) 3.11 (doublet doublet, J=5 and 1.5 cps)

of the diiodide (V) $C_{10}H_6N_2I_2$ mp 128—129° prepared by the reaction of IV with sodium iodide and hydroiodic acid in acetone solution, gave colorless liquid (VI) $C_{10}H_8N_2$, mass spectrum m/e: 156 (M^+), whose NMR spectrum showed signals as follows: 1.15 τ (2H broad singlet) 1.40 τ (2H doublet doublet, J=5 and 1.8 cps), 2.15 τ (2H doublet triplet, J=8 and 1.8 cps), 2.66 τ (2H doublet doublet, J=8 and 5 cps). From these spectra it is reasonable to assume that VI would be 3,3′-bipyridine. And VI was identified by comparison with authentic sample prepared by oxidation of *p*-phenanthroline with potassium permanganate, followed by decarboxylation.[4] Thus, the structure of III, IV and V were confirmed to be 3,3′-(4,4′-dihydroxy)-bipyridine, 3,3′-(4,4′-dichloro)bipyridine, and 3,3′-(4,4′-diiode)bipyridine, respectively.

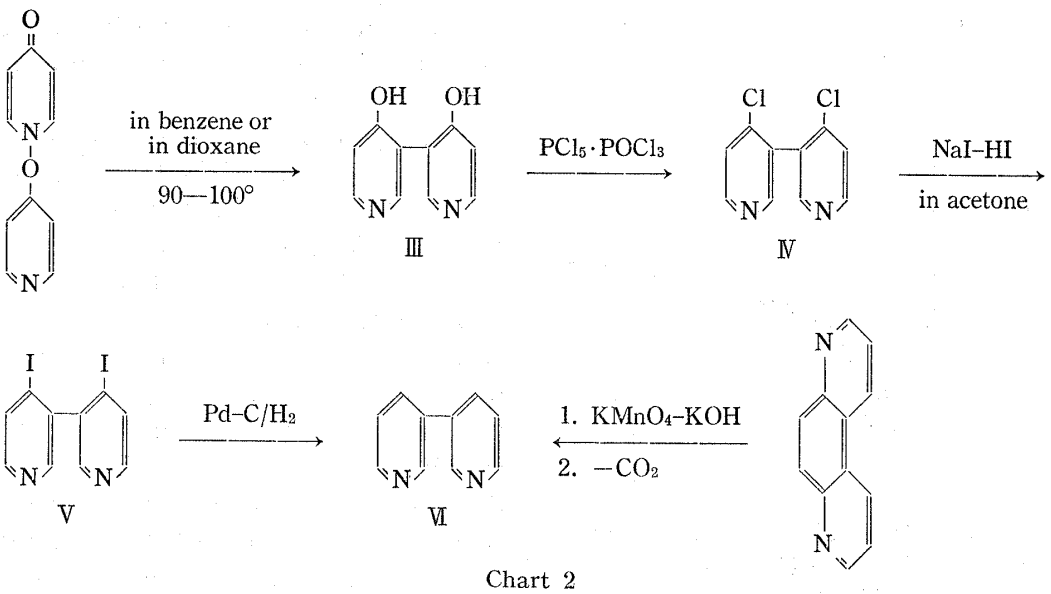
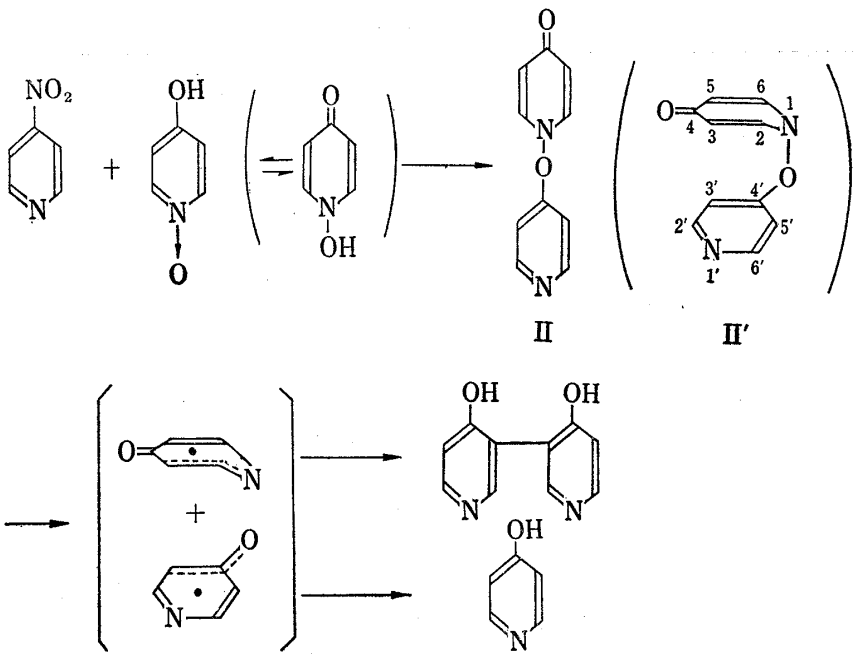


Chart 2

We present a plausible mechanism for the formation of 3,3′-(4,4′-dihydroxy)bipyridine as shown in Chart 3.

The N-oxide of 4-hydroxypyridine 1-oxide performs a nucleophilic attack on 4-position of 4-nitropyridine to give II. The intermediate II would undergo an intramolecular rearrangement to produce III by free radical way like Cope rearrangement,[5] since an ESR signal as shown in Fig. 1 was observed on a thermolysis of II. 4-Hydroxypyridine is formed by abstruction of hydrogen from solvent or substrate. This mechanism, especially in the intermediate II′ C_2—C_3 double bond comes just over C_3'—C_4' bond of pyridine ring, would rather satisfies

4) C.R. Smith, *J. Am. Chem. Soc.*, **52**, 397 (1930).
5) D.J. Cram and G.S. Hammond, "Organic Chemistry," McGrawHill, New York, p. 505. and also see; R.B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 2511 (1965) in reference to [3,3] sigmatropic reaction.



II II′

biradical intermediate

Chart 3

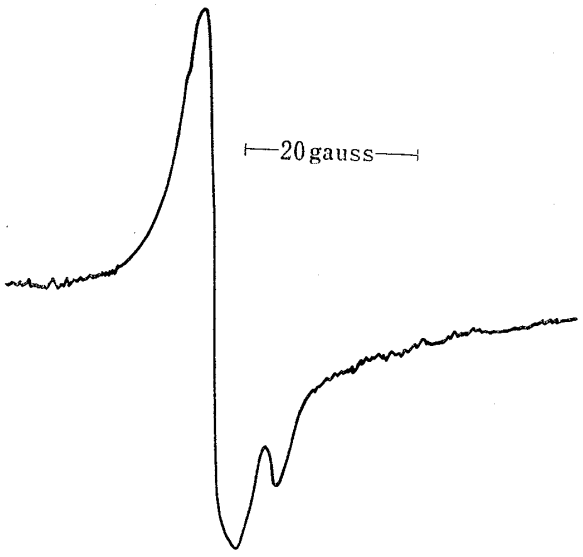


Fig. 1. Electron Spin Resonance Spectrum of the Free Radical from N-(4′-Pyridyloxy)-4-(1H)-pyridone in Benzene

the reaction mechanism for the formation of 3,3′-(4,4′-dihydroxy)biquinoline than that we have previously proposed.[1] And it would be emphasized that N–O bond in II is cloven in homolytic way.

Now, we would like to present the novel homolytic fission of N–O bond as a new source of free radical based on the results and further evidences we have in our hands.[6] N–O bond in compound having a structure of RN–OR′, would be cloven in homolytic way to produce RN· and R′O·,[7] and facility of the cleavage might depend on electron withdrawing force of both substituents R and R′. For example, N–O bond in 4-hydroxyquinoline 1-oxide was cloven at higher temperature to produce 3,3′-(4,4′-dihydroxy) biquinoline, while in the case of its O-benzoate: N-(benzoyloxy)-4(1H)quinolone, the cleavage was more easily occurred at lower temperature to produce 3,3′-(4,4′-dihydroxy) biquinoline and biphenyl.[6]

Further investigation of this series and more precise study on electron spin resonance spectroscopy of these free radicals are in progress.

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6) Details of those results will be published by us in very near future.
7) Research groups of National Cancer Center of Japan have presented similar type of homolytic fission of the N–O bond in the thermal decomposition of O,O′-diacetyl-4-hydroxyaminoquinoline 1-oxide and the report has encoureged us to promote this study. M. Araki, Y. Kawazoe, and N. Nagata, *Chem. Pharm. Bull.* (Tokyo), **17**, 1344 (1969).

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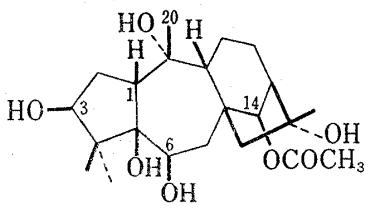
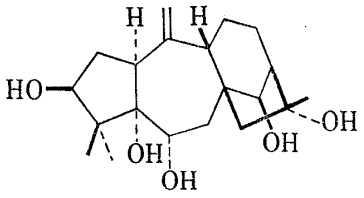
Stereochemistry of Grayanotoxins, Asebotoxins, and Rhodojaponins, Toxins of Ericaceae

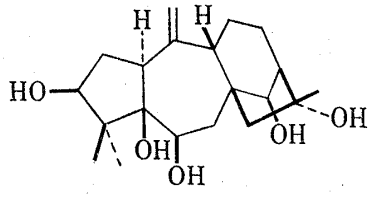
The stereochemistry of the grayanotoxins, the poisonous constituents of a number of trees belonging to Ericaceae, has been the subject of protracted controversy in recent years and indeed presents an unresolved problem in diterpenoid chemistry. Thus, Kakisawa, *et al.*[1] proposed stereoformula I for grayanotoxin I (G–I), while Kumazawa and Irie[2] allotted a conflicting stereoformula II to G–II (desacetylanhydro G–I). Recently, Matsumoto, and Watanabe[3] reconfirmed the stereostructure I for G–I and further alleged that G–I exists in the conformation A. More recently, Kumazawa and Irie[4] and Iwasa and Nakamura[5] independently proposed the revised stereoformula III for G-II through a series of chemical transformation, respectively. Quite recently, Okuno and Matsumoto[6] still implied the A/B *cis* ring junction of the G's on the basis of the ORD evidence.



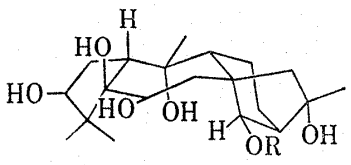
I



II



III



A

Meanwhile, we[7,8] have isolated the poisonous principles, asebotoxin I, II, and III (A–I, II, and III), and rhodojaponin I, II, and III (R–I, II, and III) from *Pieris japonica* D. DON

1) H. Kakisawa, T. Kozima, M. Yanai, and K. Nakanishi, *Tetrahedron*, **21**, 3091 (1965).
2) Z. Kumazawa and R. Irie, Abstract of the IUPAC Symposium on the Chemistry of Natural Productt, p. 43, Kyoto, April 1964.
3) T. Matsumoto and M. Watanabe, *Tetrahedron Letters*, **1968**, 6019.
4) Z. Kumazawa and R. Irie, Abstract of the Annual Meeting of the Agricultural Chemical Society of Japan, p. 137, Tokyo, April 1969.
5) J. Iwasa and Y. Nakamura, Abstract of the Annual Meeting of the Agricultural Chemical Society of Japan, p. 164, Tokyo, April 1969; *idem*, *Tetrahedron Letters*, **1969**, 3973.
6) T. Okuno and T. Matsumoto, *Tetrahedron Letters*, **1969**, 4077.
7) H. Hikino, K. Ito, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 854 (1969).
8) H. Hikino, K. Ito, T. Ohta, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 1078 (1969).