G-II 3,6-diacetate (X) ($a-49$, $[\theta]_{300}-2940$). These data demonstrate that G-XI has the andromedane skeleton. The β-configuration of the C-12 hydroxyl was deduced by the facts that 1) the $J_{11\alpha,12}$, $J_{11\beta,12}$ and $J_{12,13}$ are 6, 10, and 4 Hz, respectively, and 2) the C-17 hydrogen signal shows considerable downfield shift (−0.51 ppm) in comparison with that of G-II (VII). The combined evidence has led to the conclusion that G-XI has the stereostructure IV.

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Pharmaceutical Institute,
Tohoku University
Aobayama, Sendai

HIROSHI HIKINO
TOMIHISA OHTA
SHINJI KORIYAMA
YASUKO HIKINO
TSUNEMATSU TAKEMOTO

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Chemical Evidence for N-O Bond Fission in 4-Hydroxyaminoquinoline 1-Oxide Formation of Pyrazino[2,3-*c*:5,6-*c*′]biquinoline

In the preceding communication[1] concerning with air oxidation of 4-hydroxyaminoquinoline 1-oxide (I) (4-HAQO) in basic solution, it has been reported that pyridazino[3,4-*c*:5,6-*c*′]-biquinoline were formed in free radical way.[2-4] This paper deals with formation and its process of another type of biquinoline, pyrazino[2,3-*c*:5,6-*c*′]biquinoline from 4-HAQO.

A suspension of 4-HAQO in water was heated at 200—240° for 3 hours in a sealed tube. Chloroform soluble layer of product was subjected to chromatography on silica gel to give a new dimer (II), mp >300°, $C_{18}H_{10}N_4$, UV $\lambda_{max}^{CHCl_3}$ mμ (ε): 300(51300), 402(12100), 425(13800) and pyridazino[3,4-*c*:5,6-*c*′]biquinoline(III) in 1.5 and 4.5% yield, respectively. The structure of II was confirmed to be pyrazino[2,3-*c*:5,6-*c*′]biquinoline by comparison with an authentic sample prepared from 3-amino 4-chloroquinoline[5] as shown in Chart 1.

A research team of the National Cancer Center of Japan has reported[6] that free radical was easily produced by the thermolysis of O,O′-diacetyl 4-HAQO, probably because of the homolytic fission of N-O bond between O-acetyl and nitrogen, and further that the observed coupling constants of both nitrogen nuclei and a 3-position's proton were larger than those of other nucleis in ESR spectrum of the free radical. The report prompted us to propose plausible mechanisms as shown in Chart 2 for the formation of pyrazino- and pyridazino-biquinoline in the pyrolysis of 4-HAQO, since, it is reasonably considered that 4-HAQO at high temperature behaves as similar as its O,O′-diacetate.

1) T. Kosuge, H. Zenda, and H. Sawanishi, *Chem. Pharm. Bull.* (Tokyo), **17**, 2389 (1969).
2) C. Nagata, N. Kataoka, A. Imamura, Y. Kawazoe, and G. Chihara, *Gann*, **57**, 323 (1966).
3) N. Kataoka, A. Imamura, Y. Kawazoe, G. Chihara, and C. Nagata, *Bull. Chem. Soc. Japan*, **40**, 62 (1967).
4) N. Kataoka, S. Shibata, A. Imamura, Y. Kawazoe, G. Chihara, and C. Nagata, *Chem. Pharm. Bull.* (Tokyo), **15**, 220 (1967).
5) A. R. Surry and R. A. Cutler, *J. Am. Chem. Soc.*, **73**, 2413 (1951).
6) M. Araki, Y. Kawazoe, and C. Nagata, *Chem. Pharm. Bull.* (Tokyo), **17**, 1344 (1969). They also isolated the same compound as II in thermolysis of O,O′-diacetyl 4-HAQO (Presented at the 90 th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July, 1970).

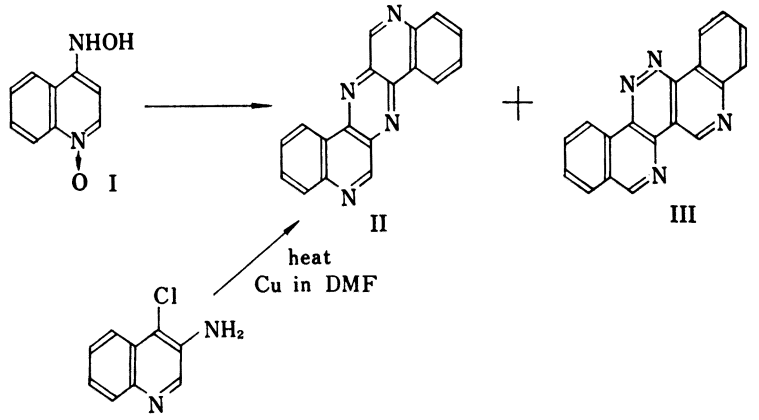
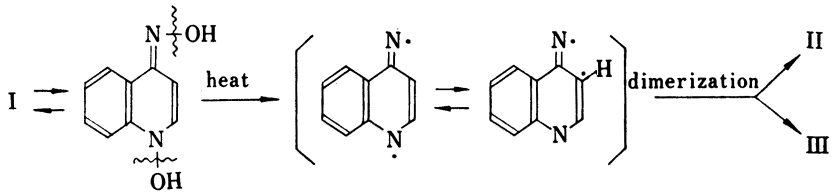


Chart 1



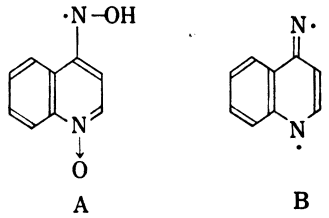


Chart 2

It has been chemically proved that N-H fissioned (A) type radical was produced by one electron oxidation of 4-HAQO in basic solution, and the above results would be direct evidence for the formation of N-O fissioned free radical (B) in 4-HAQO. Further, in the previous paper,[7] we have presented a novel understanding homolytic fission of N-O bond in a structure of RN-OR′ to produce RN· and ·OR′ under the appropriate conditions. The results obtained in this paper add another valuable information to the above presentation.

Further studies of this series and free radical reactivity 4-HAQO in relation to their carcinogenic activity are in progress.

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Shizuoka College of Pharmacy
2-2-1, Oshika, Shizuoka

Takuo Kosuge
Hiroshi Zenda
Hiroyuki Sawanishi

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7) T. Kosuge, H. Zenda, and Y. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1068 (1970).