OXIDATION OF ACETYLAMINOQUINOLINES IN UDENFRIEND'S OXIDATION SYSTEM

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Abstract —— Oxidation of 5-acetylaminoquinoline in Udenfriend's oxidation system gave 3- and 8-hydroxylated derivatives, 5,5'- azoquinoline, and three other products which are supposed to be formed via oxidative cleavage of the aromatic double bonds. The oxidation of 6- and 7-acetylaminoquinolines gave the corresponding 3-hydroxylated derivatives and 5,8-quinone derivatives.

The present study concerns with the oxidation of 5-, 6-, and 7-acetylaminoquinolines under Udenfriend's oxidation condition[1] which is known to involve a biomimetic oxidation process. As a typical experimental procedure, acetylaminoquinoline (372 mg) was suspended in 60 ml of 0.1 M phosphate buffer (pH 6.7) containing 120 mg $FeSO_4 \cdot 7H_2O$, 800 mg EDTA, and 800 mg ascorbic acid. The reaction mixture was stirred in an O_2 atmosphere for 3 h. This suspension, which had become into solution at the earlier stage of reaction, was extracted with AcOEt. The extract was evaporated to dryness in vacuo and was subjected to chromatographic separation of the products using preparative thin layer plates of Silica Gel (Merck), eluted with $CHCl_3$-CH_3OH (17:3). Nmr spectra were measured in $CDCl_3$ with a JEOL-JNM-GX400 operating at 400 MHz.

Oxidation Products of 5-Acetylaminoquinoline

The AcOEt-extract was separated into 7 components: A (Rf = 1.0, 1 mg); B (Rf = 0.65, 5 mg); C (Rf = 0.60, 5 mg); D (Rf = 0.55, 2 mg); the starting material (Rf = 0.50, 100 mg); E (Rf = 0.40, 4 mg); and F (Rf = 0.30, 2 mg).

Product A m/z: 284 (M^+ for $C_{18}H_{12}N_4$). This was identified by co-chromatography and ^{1}H-nmr with an authentic sample of 5,5'-azoquinoline prepared from 5-aminoquinoline.[2]

Product B m/z: 218.0684 (Calcd. 218.0691 for $C_{11}H_{10}N_2O_3$). Ir(KBr): 1740 and 1700 cm^{-1}. H^1-Nmr suggested that product B included (i) a 2,3-disubstituted pyridine moiety, (ii) $CH-CH_2-CHO$, and (iii) $CO-CH_3$. ^{13}C-Nmr indicated the presence of three carbonyl carbons. Long-range selective proton decoupling (LSPD) analysis[3] enabled us to deduce the structure as shown in Chart 1.

Product C m/z: 192.0534 (Calcd. 192.0534 for $C_9H_8N_2O_3$). Ir(KBr): 1730 and 1695 cm^{-1}. ^1H- and ^{13}C-nmr indicated that product C had a similar structure to product B but without a $CH-CH_2-CHO$ group. LSPD analysis suggested the structure shown in Chart 1.

Product D m/z: 177.0419 (Calcd. 177.0425 for $C_9H_7NO_3$). ^1H-Nmr consisted of signals assigned to the protons of CH(OH)-CH-CH and 2,3-disubstituted pyridine. ^{13}C-Nmr indicated the presence of one carbonyl carbon and three aliphatic CH carbons in addition to pyridine ring carbons. LSPD analysis supported the structure shown in Chart 1.

Product E m/z: 202.0760 (Calcd. 202.0742 for $C_{11}H_{10}N_2O_2$). Its nmr spectrum supported the structure to be 5-acetylamino-3-hydroxyquinoline.

Product F m/z: 202.0718 (Calcd. 202.0742 for $C_{11}H_{10}N_2O_2$). This was identified by co-chromatography and ^1H-nmr spectroscopy with an authentic sample of 5-acetylamino-8-hydroxyquinoline.[4]

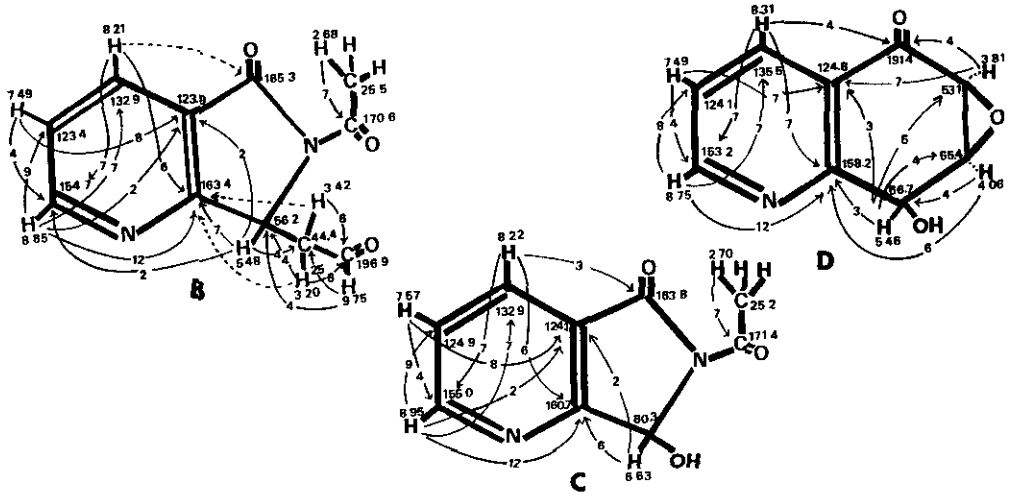
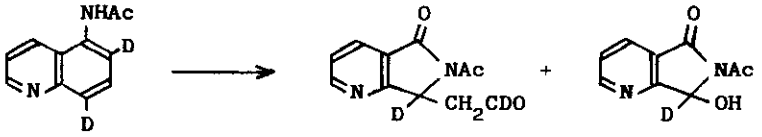


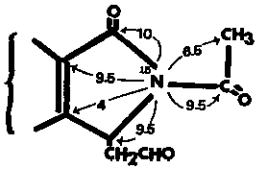
Chart 1 Chemical shifts in ppm from TMS and coupling constants in Hz. (Dotted line indicates that the coupling constant was not evaluated.)

Oxidation Products of ^{2}H- and ^{15}N-Labeled 5-Acetylaminoquinoline (Confirmation of the proposed structures of products B and C)

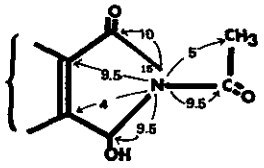
From ^{2}H-labeled 5-acetylaminoquinoline The 6,8-dideuterated derivative was synthesized by the treatment of 1 g of 5-acetylaminoquinoline dissolved in 10 ml of 70% D_2SO_4 in D_2O at 135°C for 20 h, followed by acetylation with acetic anhydride. Its nmr spectrum indicated that 6- and 8-H were completely replaced with D and that all the other ring protons, including 7-H, were proved to be intact as judged from the spectrum. On the nmr spectrum of deuterated product B, the aldehyde proton (δ, 9.75) and the CH proton (δ, 5.48) were completely missing. All the other protons were found on the spectrum along with a change in the splitting pattern from $CH\text{-}CH_2\text{-}CHO$ to $CD\text{-}CH_2\text{-}CDO$. This means that both 6- and 8-hydrogens were not exchanged with active hydrogens in the solvent during any of the reaction steps. On the nmr spectrum of deuterated product C, only the CH signal of C<u>H</u>-OH group was missing. These results suggest that the CH function in products B and C originated from the aromatic C^{8}-H.



From ^{15}N-labeled 5-acetylaminoquinoline The 5-^{15}N-acetylamino derivative of quinoline was prepared by nitration of quinoline with $^{15}N\text{-}KNO_3$ in 82% sulfuric acid,[5] followed by hydrogenation to the amino derivative and then acetylation to the labeled acetylamino derivative. The ^{13}C-NMR spectra of product B and C derived from ^{15}N-labeled material showed reasonable $^{15}N\text{-}^{13}C$ spin couplings, supporting the structural assignments of products B and C.



B



C

Oxidation Products of 6-Acetylaminoquinoline

Small amounts of two products were isolated in addition to the starting material

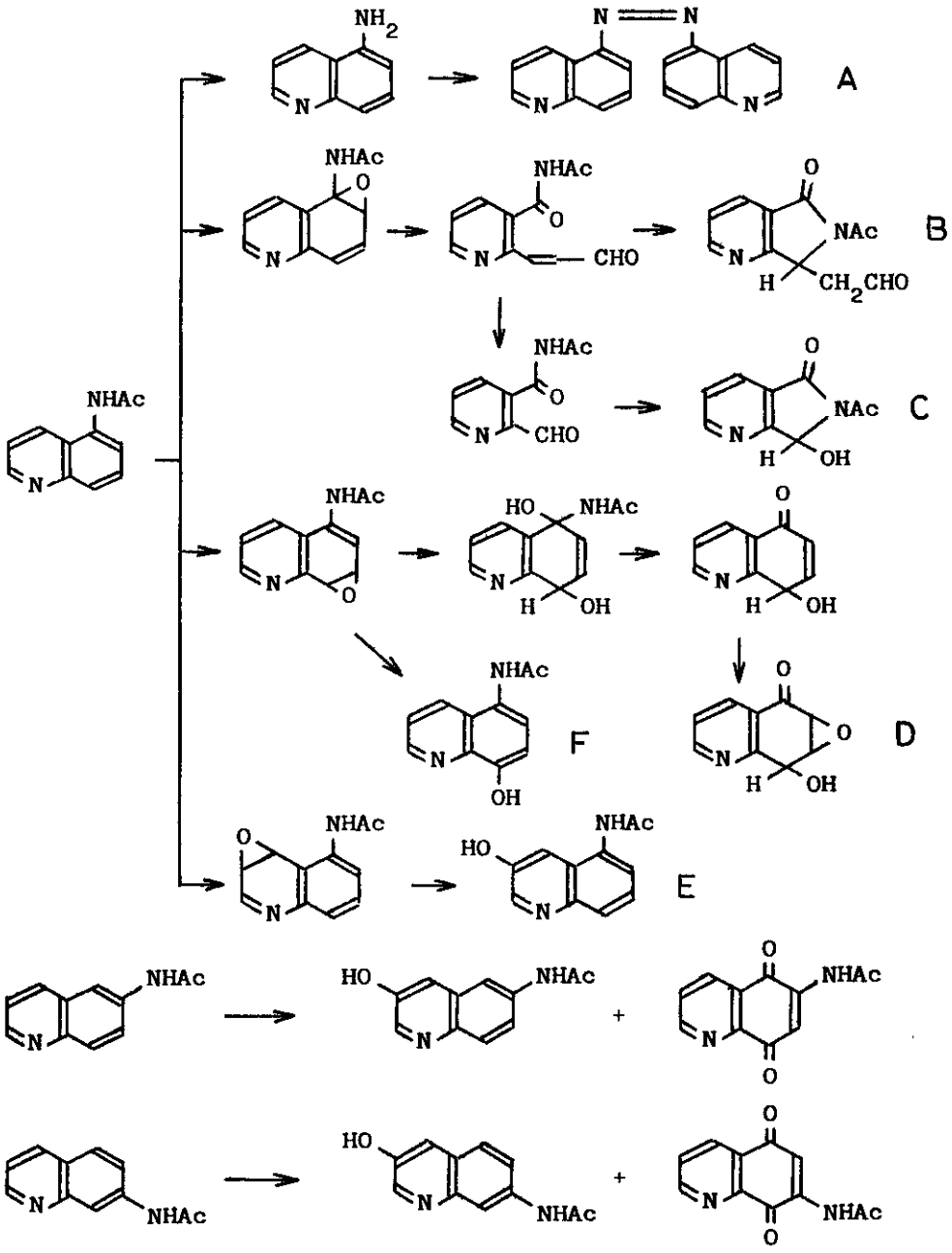


Chart 2 Products by Udenfriend's oxidation of acetylaminoquinolines and possible mechanism involved.

(Rf = 0.5). The one (Rf = 0.4) was identified by ms and nmr to be 6-acetylamino-3-hydroxyquinoline. The other (Rf = 0.6, decomp. 245°C) was identified by co-chromatography, ir, and nmr to be 6-acetylaminoquinoline-5,8-quinone which was prepared from quinoline-5,8-quinone.[6]

Oxidation Products of 7-Acetylaminoqinoline

Small amounts of two products were isolated along with the starting material (Rf = 0.5). The one (Rf = 0.4) was identified by nmr to be 7-acetylamino-3-hydroxyquinoline (m/z: 216.0552. Calcd. 216.0534 for M^+, $C_{11}H_8N_2O_3$) and the other (Rf = 0.6) was identified by nmr to be 7-acetylaminoquinoline-5,8-quinone.[6]

DISCUSSION

Biological and/or biomimetic ring oxidation of aromatic compounds is, in general, considered to be initiated by arene oxide formation. Judging from the oxidation products of 5-acetylaminoquinoline, it seems probable that the oxidation started concomitantly with its epoxidations or oxidative cleavages of the C^3– C^4, C^5– C^6, and C^7– C^8 double bonds, as illustrated in Chart 2. It is speculated for 6- and 7-acetylaminoquinoines that oxidations of both the C^5– C^6 and C^7– C^8 double bonds might result in formation of 5,8-quinones, accompanied by formation of the corresponding 3-hydroxy derivatives via epoxidation of the C^3– C^4 bond.

The products identified in the present study may be of some use as reference compounds for HPLC analysis of possible oxidative metabolites of isomeric acetylaminoquinolines in biological oxidation processes.

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