ON ACETYLATION OF 4-(N-HYDROXY-N-METHYLAMINO)QUINOLINE 1-OXIDE

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Treatment of carcinogenic and mutagenic 4-(N-hydroxy-N-methylamino)quinoline 1-oxide with acetic anhydride gave 4-(N-acetoxy-N-acetoxymethylamino)quinoline and 4-(N-acetoxy-N-methylamino)-quinoline as the main products with evolution of methane and carbon dioxide. Discussion is made in connection with the carcinogenicity and mutagenicity.

Carcinogenic and mutagenic 4-hydroxyaminoquinoline 1-oxide (I), which has 1,4-dihydroquinoline structure,[1] is acetylated with acetic anhydride to form O,O'-diacetyl derivative (I').[2] I' is partially deacetylated to 1-hydroxy-4-acetoxyimino-1,4-dihydroquinoline (I"),[1] which modifies DNA *in vitro* to give the same modified DNA bases as those obtained *in vivo* by the treatment of the cellular DNA with I.[3] Namely, 4-acyloxyaminoquinoline 1-oxide is supposed to be the active species in carcinogeneses of I and 4-nitroquinoline 1-oxide.[4] 4-Hydroxyaminoquinoline (II) gives acetylated product II', which is partially hydrolyzed to 4-acetoxyaminoquinoline (II").[5] II" is a potent carcinogen and is regarded as the model for the metabolically activated form in carcinogeneses of II and 4-nitroquinoline.[5] The present work was undertaken to prepare O-acetyl derivative of 4-(N-hydroxy-N-methylamino)quinoline 1-oxide (III). III was recently demonstrated to be potently carcinogenic.[6] Against expectation, the O-acetyl derivative of III was not found in the mixture of products obtained by the treatment with acetic anhydride. It was of interest that the crude reaction mixture thereby produced was still mutagenic on S. typhimurium TA 100, in spite that the starting material had entirely been consumed. This finding prompted us to identify the products obtained from acetylation of III.

When III was suspended in acetic anhydride at appropriate temperatures as shown

in Table I, the crystallines of III dissolved within 10 to 20 min. Its PMR spectrum indicated that III was converted to 4-(N-acetoxy-N-acetoxymethylamino)-quinoline (IV) and 4-(N-acetoxy-N-methylamino)quinoline (V) as the main products. The yields of the products are shown in Table II. The product ratio, IV/V, is markedly dependent on the reaction temperature; the yield of V increased with the reaction temperature. IV was hydrolyzed in a protic solvent such as aqueous methanol to give II" together with formaldehyde and V was hydrolyzed with dil. HCl to 4-(N-hydroxy-N-methylamino)quinoline (VI).[7] It was further noticed that carbon dioxide and methane were evolved during the reaction, and the amount of the former was found to be approximately equivalent to that of V. These results indicate that V is produced by the thermal homolysis of 1-N-OAc bond of O,O'-diacetyl derivative (VII) of III and that IV is produced from the same intermediate (VII) through a Polonovski reaction-like process.[8] Neither N-demethylation nor homolytic deoxygenation hereby observed was found in acetylations of 4-hydroxy-aminoquinoline 1-oxide (I), 4-hydroxyaminoquinoline (II), 4-(N-hydroxy-N-methyl-amino)quinoline (VI), N-methyl- and N,N-dimethyl-4-aminoquinoline 1-oxides. It seems, therefore, that these features of acetylation are characteristic of the structure of III.

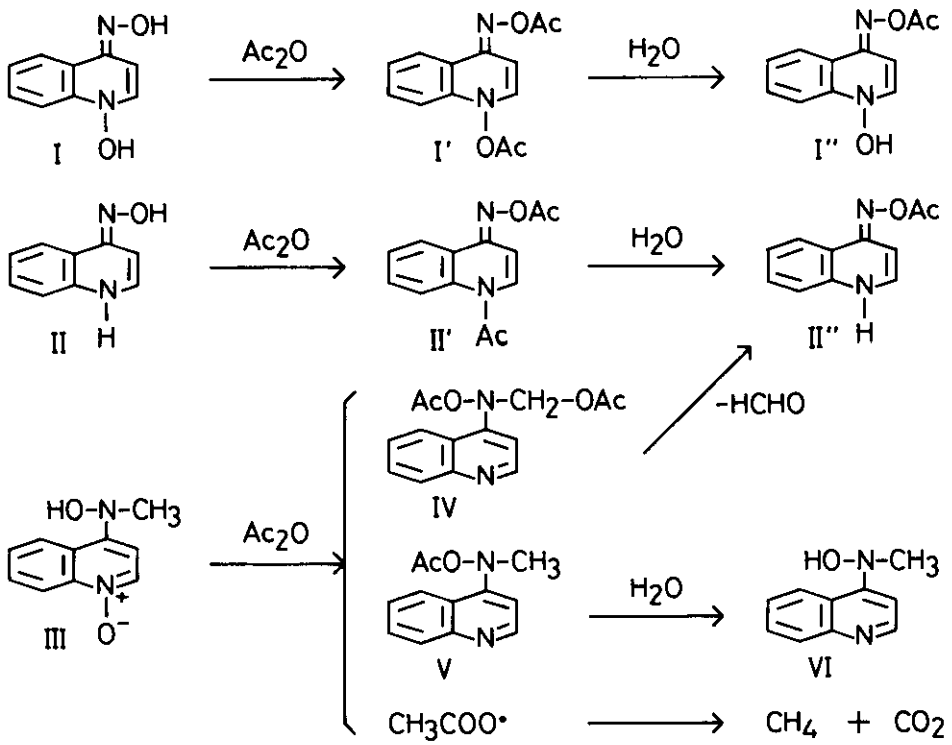

Table I. Yields of Products in Acetylation of III with Acetic Anhydride

Reaction temperature	V(%)	IV(%)	HCHO(%)*	Product ratio (IV/V)
0°	10	59	65	5.9
	10	62	65	6.2
15°	18	50	58	2.8
	17	50	54	2.9
30°	25	40	45	1.6
	27	40	44	1.5
75°	34	30	40	0.88
	30	26	37	0.87

* Analysis was made after the acid-hydrolysis of the reaction mixture.

The isolated products obtained by acetylation of III and their hydrolysis, i.e., II, II", V, and VI, were assayed for mutagenicity on Salmonella typhimurium TA 100 and it was found that II" was only mutagenic. II" is already known to be carcinogenic, too.[5] It is, therefore, possible that the carcinogenic and mutagenic activities of III are stemmed from an enzymic acylation of III, followed by the chemical degradation as described above. It is, of course, not excluded that III is activated through an alternative enzymic process to its metabolite such as a 4-(N-acyloxy-N-methylamino)quinoline 1-oxide.

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