

Radiation-induced Alkylation, Hydroxyalkylation, and Reduction of Pyridinecarboxamides in Acidic Alcoholic Solutions

Akira SUGIMORI,* Masayuki NISHIJIMA, and Hiroshi ITOH

Department of Chemistry, Faculty of Science and Technology, Sophia University,
Kioi-cho 7-1, Chiyoda-ku, Tokyo 102

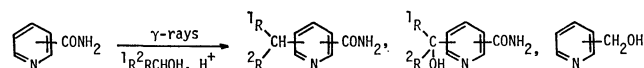
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Synopsis. The γ -irradiation of pyridinecarboxamides in acidic methanol or ethanol brings about substitution of the ring hydrogen by alkyl or hydroxyalkyl groups derived from the solvent alcohols in relatively high G -values. In 2-propanol, little alkylation and hydroxyalkylation occur and reduction of CONH_2 to CH_2OH occurs in low G -values.

In spite of their biological importance, the radiation-induced reactions of pyridinecarboxamides have not yet been thoroughly studied, at least on the basis of product analyses. Concerning the radiation-induced reactions of model compounds for NAD (nicotinamide dinucleotide), hydroxylation in aqueous solutions¹⁾ and dimer formation²⁾ have been reported. By means of pulse radiolysis technique, intermediates formed in the radiolysis of pyridinecarboxylic acid derivatives in aqueous alcohol were studied,^{3,4)} but the reports have not mentioned the structures of products. As an extension of our studies on photo- and radiation-induced reactions of pyridinecarboxylic acid derivatives,⁵⁾ we report here the radiation-induced reactions of pyridinecarboxamides, including biologically important 3-pyridinecarboxamide, in acidic alcohols. The radiation-induced reactions may furnish a useful synthetic method, owing to the specific type of reactions, which are different from those induced by a free radical initiator, and their relatively high G -values.

Results and Discussion

Gamma-irradiation of pyridinecarboxamides in acidic alcoholic solutions brings about substitution of the ring hydrogen by alkyl and hydroxyalkyl groups derived from the solvent alcohols and reduction of CONH_2 to CH_2OH .



The radiation-induced reactions of pyridinecarboxamides are very similar to those of the corresponding carboxylic esters: 1) In acidic methanolic solutions, 2- and 3-pyridinecarboxamides give methylation products in relatively high G -values. The positions for methylation in carboxamides are similar to those of the corresponding carboxylic esters. 2) In acidic methanol, 4-pyridinecarboxamide undergoes hydroxymethylation rather than methylation. 3) In acidic 2-propanol little isopropylation occurs and, instead, reduction of CONH_2 at 2- and 4-positions to CH_2OH occurs.

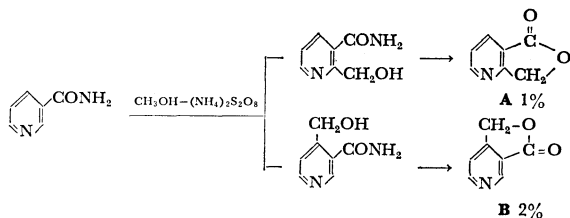
The following differences between the radiation-induced reactions of pyridinecarboxamides and those of carboxylic esters should be noted: 1) Reduction of CONH_2 at 2- and 4-positions to CH_2OH is much less efficient than that of the esters. 2) During the irradiation of 3-pyridinecarboxamide in acidic 2-propanol, 6-ethyl-3-pyridinecarboxamide was obtained in higher yield than 6-isopropyl-3-pyridinecarboxamide.

The similarities of the reactions of amides and esters suggest that the mechanism for the radiation-induced reactions of pyridinecarboxamides should be parallel to that of pyridinecarboxylic esters:⁵⁾ for alkylation and reduction, hydroxyalkyl radicals and hydrogen atom play important roles. The fact that ethylation occurs more effectively than isopropylation in γ -irradiation of 3-pyridinecarboxamide in 2-propanol suggests that $\text{CH}_3\dot{\text{C}}\text{HOH}$ radical formed by C-C cleavage of 2-propanol is more efficient for alkylation than $(\text{CH}_3)_2\dot{\text{C}}\text{OH}$ radical which is formed predominantly during γ -irradiation of 2-propanol.⁶⁾ In the free radical reaction initiated by the thermal decomposition

TABLE 1. RADIATION-INDUCED REACTIONS OF PYRIDINECARBOXAMIDES IN ACIDIC ALCOHOLIC SOLUTIONS
[Pyridinecarboxamide] = 0.03 mol dm⁻³; [H₂SO₄] = 0.05 mol dm⁻³;
dose rate, 5 × 10⁵ rad h⁻¹; dose, 1.0 × 10⁷ rad.

Substrate	Alcohol	Product (G -value)	
		Substitution product (Position and group introduced)	Reduction product
2-Pyridinecarboxamide	MeOH	4-Methyl- (0.55) 4-Methyl-6-hydroxymethyl (0.28)	
	<i>i</i> -PrOH	—	2-Pyridylmethanol (0.02)
3-Pyridinecarboxamide	MeOH	4-Methyl- (0.26) 6-Methyl- (0.97)	
	EtOH	6-Ethyl- (1.04)	
	<i>i</i> -PrOH	6-Isopropyl- (0.06) 6-Ethyl- (0.14)	
4-Pyridinecarboxamide	MeOH	2-Hydroxymethyl- (0.22)	
	<i>i</i> -PrOH	—	4-Pyridylmethanol (0.13)

of ammonium peroxodisulfate,⁷⁾ 3-pyridinecarboxamide gives 2- and 4-hydroxymethyl-3-pyridinecarboxylic acid lactones (5,7-dihydrofuro[3,4-*b*]pyridin-5-one (**A**) and 1,3-dihydrofuro[3,4-*c*]pyridin-3-one (**B**)), which are the intramolecular alcoholysis products from 2- and 4-hydroxymethyl-3-pyridinecarboxamides in low yields.



The γ -irradiation of pyridinecarboxamides and esters in methanol (and in the case of 3-pyridinecarboxamide in ethanol) gives methylation (and ethylation) products in rather high *G*-values and methylation by methanol can not be effected by an efficient free radical initiator $\text{S}_2\text{O}_8^{2-}$. Therefore, this type of radiation-induced alkylation should have synthetic utility for the introduction of alkyl groups to the pyridine nucleus.

Experimental

Materials. Commercial 2-, 3-, and 4-pyridinecarboxamides were used after the purification by recrystallization.

Gamma-irradiation. Solutions containing 0.03 mol dm^{-3} of pyridinecarboxamide and 0.05 mol dm^{-3} of H_2SO_4 were deaerated by bubbling Ar for 30 min. The solutions were irradiated at the ^{60}Co γ -facility of Japan Atomic Energy Research Institute in Takasaki (dose rate, 5×10^5 rad h^{-1} ; dose, 1.0×10^7 rad).

$(\text{NH}_4)_2\text{S}_2\text{O}_8$ -induced Reaction. A methanolic solution (50 cm^3) containing 3-pyridinecarboxamide (15 mmol), $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (15 mmol), and H_2SO_4 (0.4 cm^3) was refluxed for 30 min.

Separation of Products. The irradiated solutions were concentrated under reduced pressure and neutralized with Na_2CO_3 and NaHCO_3 . The products were separated by means of TLC (plate, Kieselgel 60 GF₂₅₄ of E. Merck Co.; developing solvents; ethyl acetate, acetone, and their mixture).

Identification of Products. 4-Methyl-2-pyridinecarboxamide: mp 119–120 °C; IR (KBr disk) 3400, 3250, 1680 and 1360 cm^{-1} ; ^1H NMR (CDCl_3) δ =8.40 (1H, d, J =4.4 Hz, H at 6-position), 8.02 (1H, d, J =1 Hz, H at 3-position), 7.23 (1H, dd, J =4.4 and 1 Hz, H at 5-position), and 2.44 (3H, s, CH_3); Found: C, 61.4; H, 6.2; N, 20.3%; Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}$: C, 61.8; H, 5.9; N, 20.6%.

6-Ethyl-3-pyridinecarboxamide: mp 161–163 °C; IR (KBr disk) 3220, 1690, 1405, 1395, and 1375 cm^{-1} ; ^1H NMR (CDCl_3) δ =8.84 (1H, d, J =2.0 Hz, H at 2-position), 8.09 (1H, dd, J =8.0 and 2.0 Hz, H at 4-position), 7.40 (1H, d, J =8.0 Hz, H at 5-position), 2.88 (2H, q, J =7.2 Hz, CH_2), and 1.30 (3H, t, J =7.2 Hz, CH_3); Found: C, 63.7; H, 6.7; N, 18.9%. Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$: C, 64.0; H, 6.7; N, 18.7%.

2-Hydroxymethyl-4-pyridinecarboxamide: mp 183–184.5

°C; IR (KBr disk) 3360, 3320, 1690, 1420, and 1040 cm^{-1} ; ^1H NMR δ =8.56 (1H, d, J =5 Hz, H at 6-position), 7.74 (1H, d, J =1 Hz, H at 3-position), 7.56 (1H, dd, J =5 and 1 Hz, H at 5-position), and 4.80 (2H, s, CH_2); Found: C, 55.0; H, 5.6; N, 19.0%. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$: C, 55.3; H, 5.3; N, 18.4%.

6-Isopropyl-3-pyridinecarboxamide (mp 135–136.5 °C) was identified only on the basis of ^1H NMR because of its low yield. ^1H NMR (D_2O) δ =8.80 (s), 8.05 (d, J =8 Hz), 7.35 (d, J =8 Hz), 3.00 (m, J =8 Hz), and 1.23 (d, J =8 Hz).

2-Hydroxymethyl-3-pyridinecarboxylic acid lactone: mp 108–111 °C; IR (KBr disk) 1760 cm^{-1} (γ -lactone C=O); ^1H NMR (CDCl_3) δ =8.85 (1H, dd, J =5.2 and 2.0 Hz, H at 6-position), 8.28 (1H, dd, J =7.6 and 2.0 Hz, H at 4-position), 7.45 (1H, dd, J =7.6 and 5.2 Hz, H at 5-position), and 5.33 (2H, s, CH_2); MS (70 eV) m/e (relative intensity) 135 (M^+ ; 58), 106 (100), 78 (38), 77 (22), and 51 (11); Found: m/e 135.0323. Calcd for $\text{C}_7\text{H}_5\text{NO}_2$: M, 135.0320.

4-Hydroxymethyl-3-pyridinecarboxylic acid lactone: mp 122–124 °C; IR (KBr disk) 1760 cm^{-1} (γ -lactone C=O); ^1H NMR (CDCl_3) δ =9.19 (1H, s, H at 2-position), 8.87 (1H, d, J =5 Hz, H at 6-position), 7.52 (1H, d, J =5 Hz, H at 5-position), and 5.38 (2H, s, CH_2); MS (70 eV) m/e (relative intensity) 135 (M^+ ; 100), 106 (66), 78 (37), and 51 (12); Found: m/e 135.0320. Calcd for $\text{C}_7\text{H}_5\text{NO}_2$: M, 135.0320.

4-Methyl-3-pyridinecarboxamide (mp 163.5–164.5 °C; lit,⁸⁾ 167–167.5 °C) and 6-methyl-3-pyridinecarboxamide (mp, 199–200 °C; lit,⁹⁾ 196–198 °C) were identified by means of melting point measurements and NMR and IR spectral analyses. Pyridylmethanols were identified by the accordance of the gas-chromatographic and spectral properties with the authentic ones.

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