[CONTRIBUTION FROM THE MELLON INSTITUTE]

Ozonolysis of Vinylpyridines

R. H. CALLIGHAN[1] AND M. H. WILT

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Ozonolysis of vinylpyridines in methanol at low temperature, followed by reduction of the active oxygen-containing products with aqueous sodium sulfite, gave pyridinecarboxaldehydes in good yields. At room temperature, the available active oxygen converted the aldehydes to pyridinecarboxylic acids. The mechanism of the ozonolysis of vinylpyridines was elucidated by the application of infrared absorption spectroscopy.

Ozonolysis of substances containing an ethylenic double bond is a common method for the preparation of aldehydes, ketones, and carboxylic acids. However, very little has been reported concerning the reaction of ozone with nitrogen heterocyclic compounds that contain an unsaturated side chain. It was of interest, therefore, to determine whether the difficultly accessible pyridinecarboxaldehydes could be obtained in good yield by the ozonolysis of vinylpyridines. In 1945, Kaslow and Stayner,[2] reported that upon ozonolysis of stilbazoles, only carboxylic acids were produced. All attempts to prepare pyridinecarboxaldehydes were unsuccessful. In 1952, Hart[3] ozonized 2-stilbazole and obtained pyridine-2-carboxaldehyde in 57% yield, but the yield was diminished if the quantities used were more than double those given (5 g.). Ozonolysis of 2-vinylpyridine was studied by Ernsdorf[4] but he obtained no pyridine-2-carboxaldehyde. Only picolinic acid and formaldehyde were isolated. In recent years, there have been many new developments in the reaction of ozone with organic compounds.[5] It seemed advisable, therefore, to re-examine the action of ozone on vinylpyridines in the light of new reactions and techniques.

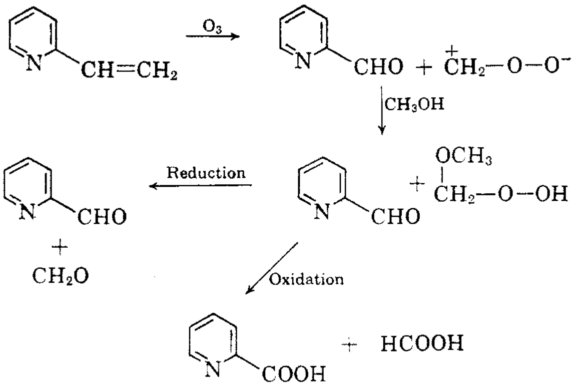
Criegee[6] and his many collaborators have shown that, in general, the ozonolysis of olefins in hydroxylic solvents gives rise to hydroperoxides in addition to a carbonyl fragment, whereas aprotic solvents allow the formation of ozonides or polymeric peroxides. In the present study, ozonolyses were conducted in methanol, which tends to stabilize the peroxidic zwitterion intermediate by reacting with it.

When a solution of a vinylpyridine in methanol was treated with one molecular equivalent of ozone at a temperature of −40°, a colorless solution resulted. Usually some ozone escaped unabsorbed during the last five minutes of the reaction, an indication that the reaction had gone to completion. Titration of the active oxygen showed that 70 to 90% of the theoretical amount was present in the solution.

Reduction of the active oxygen–containing products was accomplished by the addition of one molecular equivalent of aqueous sodium sulfite. The pyridinecarboxaldehydes were of a high degree of purity, and the infrared spectra of the aldehydes were quite similar to those of the available authentic samples. Formaldehyde was isolated as the dimedone derivative.

In general, the alkyl-substituted vinylpyridines gave higher yields of pyridinecarboxaldehydes than the unsubstituted vinylpyridines, presumably because of the decreased solubility of the alkylpyridinecarboxaldehydes in water. Apparently, some carboxylic acid was formed even at low temperature, since only 70 to 90% of the theoretical amount of active oxygen could be detected after ozonolysis.

The ozonolysis of a vinylpyridine in methanol at room temperature (+ 30°) gave a pyridinecarboxylic acid as the major product. With 4-vinylpyridine, isonicotinic acid precipitated from the solution during ozonolysis. The other pyridinecarboxylic acids were more soluble in methanol, and a solution resulted. It is believed that at ambient temperatures the basicity of the pyridine nucleus accelerates the oxidation of the pyridinecarboxaldehydes by the active oxygen.



Upon ozonolysis of unsymmetrical olefins, the double bond is cleaved in such a way as to produce a zwitterion predominantly from one particular side and the aldehyde or ketone moiety from the

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[1] To whom requests for reprints should be addressed.

[2] C. E. Kaslow and R. D. Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).

[3] E. P. Hart, *J. Chem. Soc.*, 4540 (1952).

[4] B. P. Ernsdorf, Ph.D. thesis, Stanford University (1946).

[5] Philip S. Bailey, *Chem. Revs.*, **58**, 925 (1958).

[6] R. Criegee, *Record Chem. Progr.*, **18**, 111 (1957).

TABLE I

PREPARATION OF PYRIDINECARBOXALDEHYDES

Compound Ozonized	Product	Yield, %	Oxime Derivative		Properties of the Aldehyde		
			M.p.	Lit. M.p.	B.p.	n_D^t	Specific gravity
2-Vinylpyridine	Pyridine-2-aldehyde	65	111–113	113.5[13]	181/760 mm.	$n_D^{18.5}$ 1.5389	1.126
4-Vinylpyridine	Pyridine-4-aldehyde	50	285–286[a]	282–283[14]	84/12 mm.	n_D^{25} 1.5352	1.137
2-Methyl-5-vinylpyridine	2-Methylpyridine-5-aldehyde[b]	75	160–162	New compound[c]	78/6 mm.	n_D^{25} 1.5411	1.095
5-Ethyl 2-vinylpyridine	5-Ethylpyridine-2-aldehyde	63	147–148	149–150[15]	84/5 mm.	—	—
6-Methyl-2-vinylpyridine	6-Methylpyridine-2-aldehyde	80	168–169.5	170–171[13]	M.p. 33	—	—

[a] 2,4-Dinitrophenylhydrazone. [b] *Anal.* Calcd. for C_7H_7NO: C, 69.39; H, 5.83; N, 11.57. Found: C, 69.32; H, 5.96; N, 11.83. [c] *Anal.* Calcd. for $C_7H_8N_2O$: C, 61.73; H, 5.93; N, 20.58. Found: C, 61.30; H, 6.23; N, 20.23.

TABLE II

PREPARATION OF PYRIDINECARBOXYLIC ACIDS

Compound Ozonized	Product	Yield, %	M.P.		Neutralization Equivalent	
			Observed	Lit.	Found	Calcd.
2-Vinylpyridine	Picolinic acid	62	136–137	136–136.5[2]	124	123
4-Vinylpyridine	Isonicotinic acid	61	308–310	309–310[2]	124	123
2-Methyl-5-vinylpyridine	2-Methylpyridine-5-carboxylic acid	40	208–210	209–210[16]	139	137
5-Ethyl-2-vinylpyridine	5-Ethylpicolinic acid	40[a]	—	—	—	—
6-Methyl-2-vinylpyridine	6-Methylpicolinic acid	62	128–130	126–127[17]	136	137

[a] Two molecular equivalents of ozone was used. Isolated as copper salt. *Anal.* Calcd. for $C_{16}H_{16}N_2O_4Cu$: C, 52.75; H, 4.4; N, 7.7. Found: C, 52.71; H, 4.5; N, 7.65.

other.[7] It was of interest, therefore, to determine whether ozone cleaved vinylpyridines to give pyridinecarboxaldehydes plus an alkyl zwitterion or formaldehyde plus a pyridyl-containing zwitterion. On the basis of infrared absorption spectroscopy in the ozonolysis of 2-vinylpyridine, the mechanism of the reaction is considered to proceed as shown.

EXPERIMENTAL[8]

The 2-vinylpyridine, 4-vinylpyridine, and 5-ethyl-2-vinylpyridine used in this work were obtained from the Reilly Tar and Chemical Corp. The 6-methyl-2-vinylpyridine was obtained from K and K Laboratories, Inc., and the 2-methyl-5-vinylpyridine was obtained from the Chemical Division of the Borden Co. All the vinylpyridines used were of 95% minimum purity. The solvent was Carbide and Carbon Chemicals Co. methanol of above 99% purity. Other reagents mentioned were of the purest quality obtainable. The ozonator and accessory equipment have been described previously.[9]

Preparation of pyridine-2-carboxaldehyde (general procedure). A solution of 2-vinylpyridine (10.5 g., 0.1 mole) in methanol (100 ml.) was treated with approximately 2.3 weight % ozone (in oxygen) at a temperature of −40° (Dry Ice–ethanol bath) and at a flow rate of 102 l./hr. for 1 hr. and 33 min. Under these conditions, 4.8 g. (0.1 mole) of ozone was passed into the solution. A small amount of ozone was unabsorbed during the last 5 min. of the reaction. The reaction mixture gave a positive test for hydroperoxide[10] and a negative test for hydrogen peroxide.[11] To the cold, colorless solution was added immediately a solution of sodium sulfite (12.6 g., 0.1 mole) in 75 ml. of water. An exothermic reaction occurred, and the temperature rose to 40°. After cooling to room temperature, the methanol was evaporated in a stream of air. Saturated sodium chloride solution (25 ml.) was added, and the aqueous solution was extracted with six 25-ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated to dryness on a steam bath. The residue was further dried in a vacuum desiccator, yielding 7.0 g. (65.3% yield) of pyridine-2-carboxaldehyde. Formaldehyde was isolated from the remaining aqueous solution by formation of the dimedone derivative, which melted at 188–190°; lit.[12] m.p. 189°.

Results from the ozonolysis of a number of vinylpyridines are summarized in Table I. The infrared spectra of the product aldehydes were very similar to the spectra of authentic materials, which had a purity of greater than 98% when examined by vapor phase chromatography. The product alde-

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(7) P. S. Bailey and S. Bath, *J. Am. Chem. Soc.*, **79**, 3120 (1957).

(8) Melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectrophotometer fitted with a sodium chloride prism. Elemental analyses were performed by the Mellon Institute Microanalytical Laboratory.

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(10) R. Criegee, *Fortschr. chem. Forsch.*, **1**, 536 (1950).

(11) W. C. Schumb, C. N. Satterfield, and R. L. Wentworth, A.C.S. Monograph No. 128, *Hydrogen Peroxide*, Reinhold Publishing Corp., New York, 1955, p. 549.

(12) A. I. Vogel, *Practical Organic Chemistry*, 3rd ed., Longmans Green and Co., London, 1956, p. 334.

(13) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

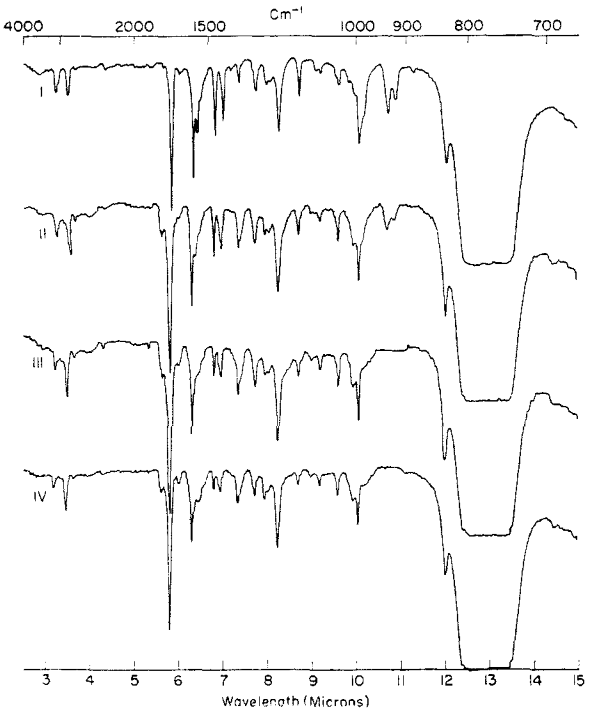
(14) E. H. Rodd, *Chemistry of Carbon Compounds*, Vol. IV, Part A, "Heterocyclic Compounds," 1st ed., Elsevier Publishing Co., New York, 1957, p. 553.

(15) W. Mathes and W. Sauermilch, *Chemiker-Ztg.*, **80**, 475 (1956).

hydes had purities of greater than 90% when examined by the same technique. The high purities of the crude products were not unanticipated because of the selective nature of the ozone attack on double bonds and because the procedure used in isolation of the aldehydes removed the carboxylic acids, which were the major side product.

Preparation of picolinic acid (general procedure). A solution of 2-vinylpyridine (10.5 g., 0.1 mole) in methanol (100 ml.) was treated with approximately 2.3 weight % ozone (in oxygen) at room temperature (+ 30°) and at a flow rate of 102 l./hr. for 1 hr. and 33 min. Under these conditions, 4.8 g. (0.1 mole) of ozone was passed into the solution. All the ozone was absorbed, and during the last 5 min., the light yellow solution became colorless. After flushing with oxygen for 5 min. to remove dissolved ozone, the solution was transferred into a 500-ml. round-bottom flask and the methanol removed in a flash evaporator at a temperature of 50°. The residue consisted of a white solid plus some oil and smelled strongly of formaldehyde. Methyl ethyl ketone (50 ml.) was added, and the solids were dispersed and filtered to yield 6.4 g. of picolinic acid which melted at 136–137°; lit.[2], m.p. 136–136.5°. Benzene was added to the filtrate, and it was further evaporated to yield an additional 1.2 g. of crude acid which melted at 132–135°. A total of 7.6 g. was obtained, which represents a 62% yield. The infrared spectrum of the acid as isolated was identical with that of an authentic sample obtained from Eastman Kodak Co. Results from the preparation of other pyridinecarboxylic acids are summarized in Table II.

In an effort to determine the mechanism of the ozonolysis, a mixture of 2-vinylpyridine and pyridine-2-carboxaldehyde was dissolved in carbon tetrachloride and ozonized. Figure 1 shows that when a 2-vinylpyridine solution containing pyridine-2-carboxaldehyde (spectrum I) is ozonized, the carbonyl band (5.8 to 6.0 μ) due to the aldehyde does not disappear but becomes much stronger (spectrum II). Therefore, there must have been produced a material with a carbonyl band that shows the same frequency as that of pyridine-2-carboxaldehyde. A further increase in the carbonyl band of pyridine-2-carboxaldehyde is seen after 90% ozonolysis (spectrum III). After 110% ozonolysis, the carbonyl band of pyridine-2-carboxaldehyde begins to disappear, presumably because of the formation of picolinic acid, which is insoluble in carbon tetrachloride and precipitates from the solution. The addition of gaseous formaldehyde to a solution of pyridine-2-carboxaldehyde did not cause an increase in the infrared absorption in the carbonyl band of pyridine-2-carboxaldehyde, which demonstrates that the increased absorption which was observed was due to the formation of pyridine-2-carboxaldehyde. Formaldehyde in carbon tetrachloride apparently polymerizes quite rapidly and precipitates.



I. Nonozonized 0.1M 2-vinylpyridine and 0.1M pyridine 2-carboxaldehyde solution.
II. About 50% ozonized 0.1M 2-vinylpyridine and 0.1M pyridine-2-carboxaldehyde solution.
III. About 90% ozonized 0.1M 2-vinylpyridine and 0.1M pyridine-2-carboxaldehyde solution.
IV. About 110% ozonized 0.1M 2-vinylpyridine and 0.1M pyridine-2-carboxaldehyde solution.

Fig. 1. Spectra of various concentrations of 2-vinylpyridine and pyridine-2-carboxaldehyde in carbon tetrachloride.

These data clearly indicate that ozone cleaves vinylpyridines to produce pyridinecarboxaldehydes and an alkyl zwitterion.

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PITTSBURGH 13, PA.

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(16) E. C. Kooyman and J. P. Wibaut, *Rec. trav. chim.*, 65, 10 (1946).

(17) W. Mathes, W. Sauermilch, and T. Klein, *Chem. Ber.*, 86, 584 (1953).