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# Oxidation of 2-Ethyl-3,5-dimethylpyridine to Dinicotinic Acid

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2,3,5-Trialkylpyridines have recently (2) become available in good yield, based on a catalytic synthesis from aldehydes and ammonia. The product from propanol, 2-ethyl-3,5-dimethylpyridine, is of particular interest, since its synthesis can be based on the inexpensive raw materials: ethylene, synthesis gas and ammonia. The dehydrogenation of this compound to the corresponding vinylpyridine has already been reported (3). We have now found that 2-ethyl-3,5-dimethylpyridine can be oxidized to dinicotinic acid in excellent yields. A number of oxidation systems for pyridinecarboxylic acids have been described in the literature (4), mainly using the picolines, 2-methyl-5-ethylpyridine or quinoline. We have examined several of these systems with the best yields being obtained with selenium catalyzed sulfuric acid oxidation.

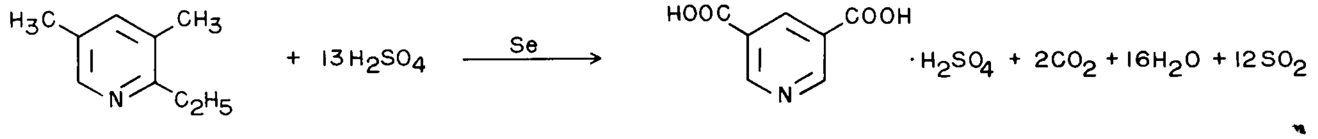
The selenium-catalyzed sulfuric acid oxidation to pyridinecarboxylic acid has been reported for a number of pyridine derivatives (5,6) in yields up to about 80%. The chemistry of the reaction probably involves oxidation by selenium dioxide followed by reoxidation of the selenium metal with sulfuric acid, since good yields have been reported (7) for the oxidation of alkylpyridines with stoichiometric amounts of selenium dioxide, and it is known that concentrated sulfuric acid will oxidize selenium metal to selenium dioxide. Under the conditions employed here (> 300°) the product expected from 2-ethyl-3,5-dimethylpyridine is dinicotinic acid. The 2,3,5-tricarboxylic acid is probably formed first but decarboxylation takes place immediately, since 2,3,5-tricarboxylic acid decarboxylates to dinicotinic acid already at 150° (8).

The laboratory-scale reactions were carried out in glass flasks at atmospheric pressure. The volatile oxidation products (water, carbon dioxide, sulfur dioxide) were distilled out continuously and the aqueous phase condensed. After the reaction was complete, the excess sulfuric acid was distilled under reduced pressure, the dinicotinic acid hydrosulfate was dissolved in water and the solution neutralized with base to *p*H 2.3, whereupon the free dinicotinic acid was precipitated. The best yield obtained was 88%. Figure 1 shows the effect of catalyst concentration on the yield. Good yields were obtained at about 0.1 mole selenium per mole pyridine. Figure 2 shows how the reaction proceeds with time.

The above experiments were carried out with excess sulfuric acid (20 moles/mole pyridine, theory, 13). About 1 mole was recovered in the vacuum distillation. Lower yields were obtained where less acid was used. Other operating conditions also effect the yield. When 800 g. of sulfuric acid was used with 12.8 g. of selenium dioxide and the contents heated quickly to 375° for 1 hour, a yield of 17% of nicotinic acid, 25% of 5-methylnicotinic acid and 17% of dinicotinic acid was obtained. In an effort to reduce the amount of acid required for oxidation, air was blown through the mixture during the reaction. However, this produced large amounts of tar and coke. Cupric chloride and ferric chloride were also tried to aid this air oxidation but no better results were obtained.

Certain other pyridines were also of interest. 4-Ethyl-3,5-dimethylpyridine and 3,5-dimethylpyridine are by-products in the pyridine synthesis. In analogous experiments 3,5-dimethylpyridine gave dinicotinic acid in 72% yield, while 4-ethyl-3,5-dimethylpyridine gave 50% of dinicotinic acid. This lower yield was probably due to the much slower decarboxylation in the 4-position. The 3,4,5-pyridinetricarboxylic acid was not isolated since it was probably soluble at *p*H 2.3, whereas dinicotinic acid precipitates out. The analysis of the precipitate was in very good agreement with dinicotinic acid. 2-Propyl-3,5-diethylpyridine, made from butyraldehyde, was also oxidized with this system. The yield of dinicotinic acid was 84%.

Other oxidation systems which gave lower yields with 2-ethyl-3,5-dimethylpyridine included: tellurium-catalyzed sulfuric acid, molybdenum-catalyzed nitric acid - sulfuric acid, autoclave oxidation with dilute



nitric acid, copper nitrate or sodium dichromate, and catalytic air oxidation with bismuth molybdate, bismuth phosphate and cobalt molybdate.

Preliminary experiments indicated that dinicotinic acid could be decarboxylated to nicotinic acid in 65% yield after 21 hours at 256° using 2-propyl-3,5-diethylpyridine as solvent. This yield can probably be improved with better decarboxylation conditions.

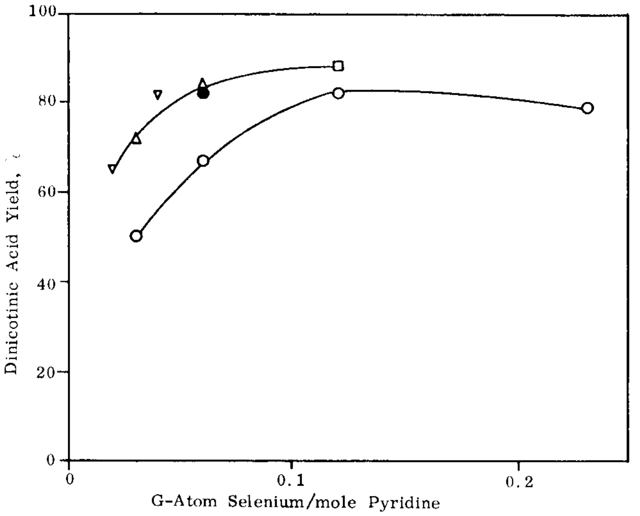


Figure 1. Oxidation of 2-Ethyl-3,5-Dimethylpyridine (0.5 mole)

| Se | $SeO_2$ | Pre-loading of Reaction Flask | Added after Flask heated to 300° | Added after 150 ml. $H_2O$ condensed |
|---|---|---|---|---|
| □ | ○ | 4 moles $H_2SO_4$<br>25% of $SeO_2$/Se | 4 moles $H_2SO_4$<br>25% of $SeO_2$/Se<br>0.5 mole EDP | 2 moles $H_2SO_4$<br>50% of $SeO_2$/Se |
| △ | ● | 4 moles $H_2SO_4$<br>50% of $SeO_2$/Se | 4 moles $H_2SO_4$<br>50% of $SeO_2$/Se<br>0.5 mole EDP | 2 moles $H_2SO_4$ |
| ▽ | | 6 moles $H_2SO_4$ | 4 moles $H_2SO_4$<br>100% of Se<br>0.5 mole EDP | ------------- |

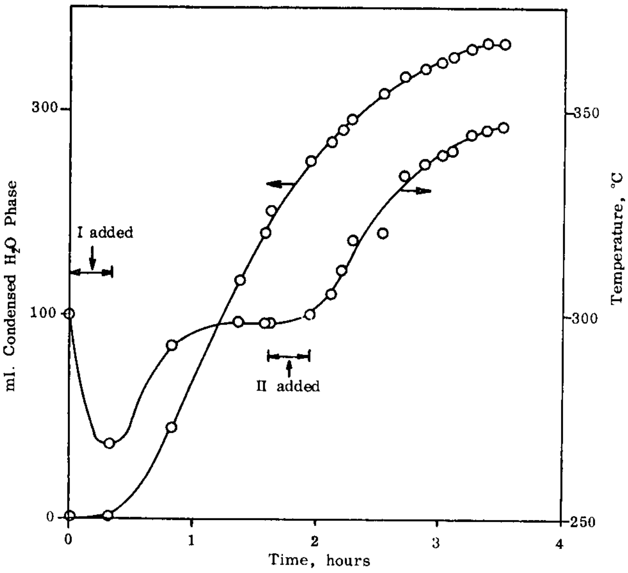


Figure 2. Oxidation of 2-Ethyl-3,5-Dimethylpyridine (0.5 mole)

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Reaction Flask Pre-filled with 400 g. $H_2SO_4$, 1.14 g. Se

I = 400 g. $H_2SO_4$, 67.5 g. EDP, 1.14 g. Se

II = 200 g. $H_2SO_4$, 2.28 g. Se

## EXPERIMENTAL

Oxidation with Selenium-Catalyzed Sulfuric Acid.

Selenium (1.4 g.) and 95% sulfuric acid (400 g.) were placed in a glass round-bottom flask equipped with an offset condenser and heated to 300° (time-temperature profile given in figure 2). A mixture of 400 g. of sulfuric acid, 1.14 g. of selenium and 67 g. of 2-ethyl-3,5-dimethylpyridine was added dropwise during 30 minutes. After 150 ml. of the aqueous phase had condensed out, 200 g. of sulfuric acid and 2.28 g. of selenium were added (ml. of water-time profile given in figure 2). The reaction was stopped after 3 hours and 10 minutes. Sulfuric acid (81.4 g.) was vacuum distilled from the yellow reaction product (228.5 g.). The distillation residue (144 g.) was dissolved in water and the *p*H adjusted to 2.3 with ammonium hydroxide. The precipitated dinicotinic acid was removed by filtration and dried at 120°, yield, 73 g. (88%); m.p. 331-333° (Lit. 320-323°).

*Anal.* Calcd. for $C_7H_5NO_4$: C, 50.00; H, 3.59; N, 8.33; MW, 167.12; Acid value, 83.6. Found: C, 50.2; H, 3.1; N, 8.3; MW, 167; Acid value, 84.

The NMR spectrum (in perdeuterodimethylsulfoxide) showed two $\alpha$-protons and one $\gamma$-proton.

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