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# ON THE REACTION OF NITRO-FURFURAL DERIVATIVES AND AMMONIUM SULFATE

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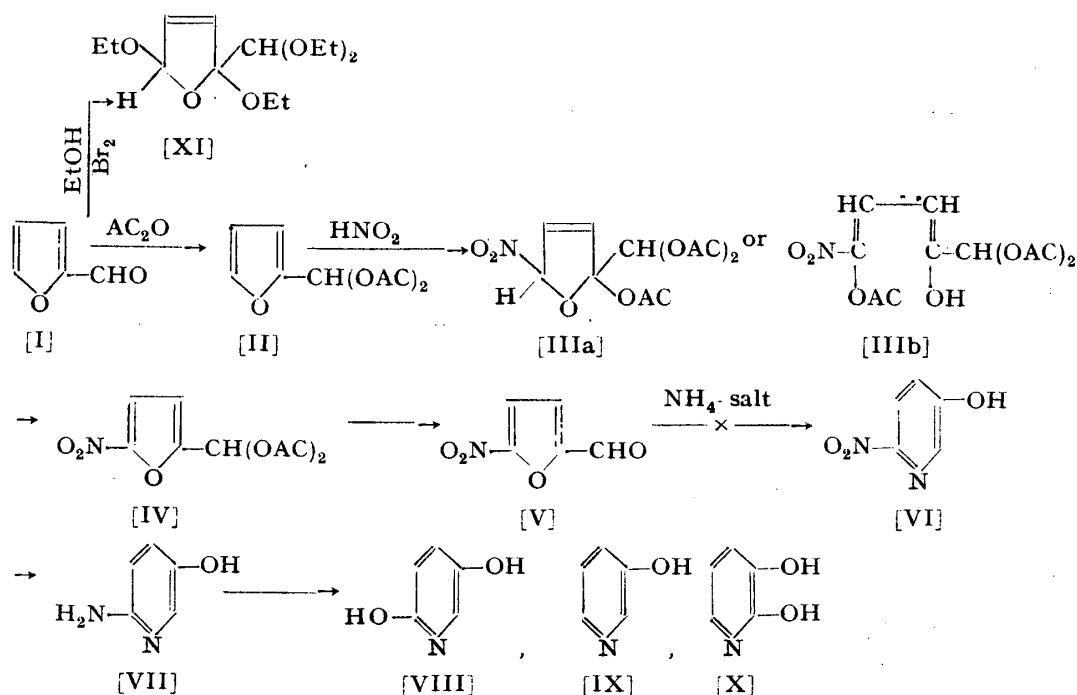
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Aso (1) previously reported that various kinds of  $\beta$ -hydroxy-pyridine derivatives had been obtained from furfural derivatives and ammonium salts.

The present investigation was subjected to a similar reaction in the hope that 2-nitro-5-hydroxy-pyridine [VI] might result from 5-nitro-furfural [V] (2) according to the formation mechanism previously described and that 2,5-dihydroxy-pyridine [VIII] might be synthesized from VI by reduction and diazo-reaction, but the desired 2-nitro-5-hydroxy-pyridine was not synthesized.



In 1950, Den Hertog *et al.* (3) reported that VIII was synthesized from diethoxy-pyridine by another method.

Unexpectedly, we found that the reactions of nitro-furfural derivatives and

ammonium salts differ from that of furfural derivatives in their properties. From the results of this experiment, both furfural [I] and furfural diacetate [II] produced 3-hydroxy-pyridine [IX] by reacting with ammonium sulfate, and 2,3-dihydroxy-pyridine [X] by reacting with hydroxylamine-hydrochloride, while similar reaction products of 5-nitro furfural diacetate [IV] and 5-nitro-furfural [V] with ammonium sulfate were succinic and fumaric amide, and also the reaction product with hydroxylamine-hydrochloride was 5-nitro-furfural-oxime. On the other hand, the intermediate [III] of 5-nitro-furfural diacetate produced X by reacting with ammonium sulfate, but did not produce pyridine derivatives by reacting with hydroxylamine-hydrochloride. From the above facts, considering the differential structures of III (III a and IIIb) (4), we took up diethoxy-dihydrofurfural diethylacetal [XI] containing the structure similar to IIIa, and xylouronic acid similar to IIIb.

Similarly as III, XI produced X by reaction with ammonium sulfate, but did not produce pyridine derivatives by reaction with hydroxylamine-hydrochloride, and also xylouronic acid did not produce pyridine derivatives. It is thought that the formation mechanism of X from III or XI may have some relation to the formation mechanism of X from sugar and ammonium salts (1).

### Experimental

[A] 5-Nitrofurfural was prepared by the usual method except that the transformation of 5-nitro-furfural diacetate was modified from the method of H. Gilman.

#### (a) *Furfural diacetate (II)*

Acetic anhydride 153 g (1.5 M) and stannous chloride 1.6 g were added in a 1 liter three-necked flask equipped with a mechanical stirrer, dropping funnel and thermometer, and cooled from  $-5^{\circ}\text{C}$  to  $-10^{\circ}\text{C}$ , and then 96 g (1 M) of the cooled furfural was added with stirring at such a rate that the temperature did not exceed  $-2^{\circ}\text{C}$ . After addition was complete, stirring was continued for 1 hr, the reaction mixture was placed in an ice-box over night. The reaction mixture was poured into 800 ml of ice and water, and sodium carbonate solution was added until the oil was coagulated. The product was filtered by suction, dried and distilled under reduced pressure, b.p.  $110\sim 112^{\circ}\text{C}/4\text{ mm Hg}$ , the melting point of purified product was  $52\sim 53^{\circ}\text{C}$ . Yield 160 g (80%).

#### (b) *The intermediate of 5-nitro-furfural diacetate (III)*

The nitrating mixture was prepared by adding dropwise 110 g of fuming nitric acid (sp. gr. 1.5) to 240 g (2.3 M) of acetic anhydride cooled to  $-5^{\circ}\text{C}$ , and then 1 g of conc. sulfuric acid as the acid catalyser.

A solution of 80 g (0.4 M) of furfural diacetate in 90 g of acetic anhydride was added slowly to the nitrating mixture which was not allowed to rise above  $0^{\circ}\text{C}$ .

After addition was complete, stirring was continued for 2 hrs, keeping below 2°C. It was poured into about 2 kg of cracked ice, and then sodium hydroxide solution (about 40 %) was added with vigorous stirring until the precipitation of oil was complete, when the solution was pH 3.4~3.8.

The precipitated heavy oil (yellowish brown) was the intermediate of 5-nitro-furfural diacetate. When it was cooled, crystallized, melted at 96~97°C, and when it was recrystallized from petroleum ether benzene mixture, it melted at 106~107°C.

(c) *5-Nitro-furfural diacetate (IV)*

The solution which was regulated to pH 3.4~3.8, containing the heavy oil described above, was kept at 55°C for 2 hrs, and stood until precipitation was complete with occasional stirring. The precipitate was filtered by suction, and washed with water. When it was recrystallized from hot alcohol, it melted at 92~93°C. Yield 87 g (88%).

(d) *5-Nitro-furfural (V)*

In an atmosphere of carbon oxide, 145 g of 5-nitro-furfural diacetate (0.6 M) was refluxed, with continuous stirring, with a solution of 300 g of conc. sulfuric acid in 600 ml of water at 80~90°C for 20 minutes. The ether extract of the cooled hydrolysate was washed with water, dried over sodium sulfate and then distilled at 128~132°C/10 mmHg. When it was cooled, and crystallized, it melted at 35~36°C. Yield 67 g (80%).

[B] *Reaction of furfural derivatives with ammonium sulfate or hydroxyl-amine-hydrochloride.*

The procedures used for the present experiments were essentially the same as those described in the previous papers in this journal (1).

Nitro-furfural derivatives were so unstable that the reaction mixture was exploded in an autoclaved procedure, so it was very difficult to obtain the reaction products (5). It was due to the unstability of nitro-furfural derivatives that we could not clearly explain the reaction of nitro-furfural derivatives and ammonium salts.

General procedure ; furfural derivative 5 g, ammonium sulfate 3 g and 50 ml of water were heated in an autoclave at 150~155°C (about 5 atm) for 3 hrs. After cooling, the reaction mixture was filtered, concentrated to about half of the original volume under reduced pressure, and extracted with ether in acidic side, and then alkalified with sodium carbonate, extracted again with ether.

(1) By heating furfural 5 g, ammonium sulfate 3.4 g and water 50 ml, 3-hydroxy-pyridine, 0.3 g of a colorless prism melting at 127°C, was obtained from ether extract in alkaline side. In acidic side, a small amount of succinic and fumaric acid were obtained.

(2) By similarly heating furfural diacetate 5 g, ammonium sulfate 3 g and

water 50 ml, 0.3 g of 3-hydroxy-pyridine was obtained.

(3) By heating with hydroxylamine-hydrochloride 2 g, both furfural 5 g and furfural diacetate 5 g produced 2,3-dihydroxy-pyridine 0.2 g similarly.

(4) From the intermediate of 5-nitro-furfural diacetate 5 g, ammonium sulfate 2 g and water 50 ml, a crystal melting at 183°C was obtained from ether extract in acidic side. The mixture of the obtained crystal and succinic acid gave no depression of melting point. Yield 0.2 g.

Microanalysis	Found	C %	40.98, 40.79;	H %	4.94, 4.99
	Calcd. for C <sub>4</sub> H <sub>6</sub> O <sub>4</sub>	C %	40.68	H %	5.08

In alkaline side, 0.3 g of a colorless crystal melting at 240°C was obtained, and recrystallized from benzene by the aid of charcoal. It was a colorless prism melting at 245~247°C. It gave a deep blue color by FeCl<sub>3</sub> and a deep green color by Folin-Denis reagent. It was shown to be C<sub>5</sub>H<sub>5</sub>O<sub>2</sub>N by analysis, and the melting point of this substance was not depressed by admixture with the authentic 2,3-dihydroxy-pyridine.

Microanalysis	Found	C %	54.36, 54.06;	H %	4.69, 5.01;	N %	12.52
	Calcd. for C <sub>5</sub> H <sub>5</sub> O <sub>2</sub> N	C %	54.05	H %	4.50	N %	12.60

Its monoacetate was a colorless needle, mp. 150~153°C.

(5) From the intermediate of 5-nitro-furfural diacetate 5 g and hydroxylamine-hydrochloride 2 g, a crystal melting at 235~240°C was obtained from the ether extract in acidic side; yield 0.2 g. It was recognized to be a mixture of succinic and fumaric acid by the application of paper partition chromatography. In alkaline side, nothing was obtained.

(6) Formation of ammonia from the intermediate and water

By heating the intermediate of 5-nitro-furfural diacetate 5 g and water 50 ml, 0.1 g of fumaric acid was obtained from the ether extract in acidic side. In alkaline side, the syrup which indicated a deep blue color by FeCl<sub>3</sub> and a deep green color by Folin-Denis reagent was obtained, but no crystalline derivatives could be isolated from this fraction. On the formation of ammonia in the reaction mixture, it was determined by the method of Kjeldahl that the residual amounts of ammonia were 74 mg.

(7) By similarly heating 5-nitro-furfural diacetate 5 g, ammonium sulfate 3 g and water 50 ml, a mixture of succinic and fumaric acid was obtained from ether extract in acidic side. When it was alkalified with sodium carbonate and extracted with ether, a crystal melting at 105~110°C was obtained, yield 0.1 g. This crystal showed no color reaction with FeCl<sub>3</sub>. Its formula corresponded to C<sub>6</sub>H<sub>7</sub>O<sub>4</sub>N<sub>2</sub>, but the hydrolysate which was subjected to hydrolyse by 5% hydrochloric acid for 2.5 hrs gave a crystalline material melting at 176°C and the main portion of hydrolysate was succinic acid, but it contaminated with a trace of fumaric acid.

Microanalysis	Found	C %	42.10, 42.20;	H %	4.11, 3.51;	N %	16.01, 16.02
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Calcd. for  $C_6H_7O_4N_2$  C% 42.10 ; H % 4.09 ; N % 16.33

(8) By heating 5-nitro-furfural 5 g, ammonium sulfate 3 g and water 50 ml, the same product as described above was obtained, but pyridine derivatives presumed were not obtained.

(9) By heating 5-nitro-furfural diacetate 5 g with hydroxylamine-hydrochloride 2 g, 5-nitro-furfuraloxime melting at  $125^{\circ}\text{C}$  was obtained quantitatively. By similarly treating 5-nitro-furfural, only its oxime was obtained.

(10) From diethoxy-dihydrofurfural diethylacetal 10 g, ammonium sulfate 4 g and water 100 ml, a crystal melting at  $183\sim 185^{\circ}\text{C}$  was obtained from the ether extract in acidic side, and identified to be a mixture of succinic and fumaric acid by the application of paper partition chromatography.

In alkaline side, 0.5 g of a colorless prism melting at  $240\sim 243^{\circ}\text{C}$  was obtained. It recrystallized from benzene by the aid of charcoal, melted at  $245\sim 247^{\circ}\text{C}$ , and the mixture of the obtained crystal and the authentic 2,3-dihydroxy-pyridine gave no depression of melting point.

(11) By heating diethoxy-dihydrofurfural diethylacetal 5 g, hydroxylamine-hydrochloride 2 g and water 50 ml, succinic and fumaric acid were obtained from the ether extract in acidic side, but nothing was obtained in alkaline side.

(12) By similar procedure, from xylouronic acid 5 g, ammonium sulfate 3 g and water 50 ml, a small amount of syrup which indicated a deep blue color by  $\text{FeCl}_3$  was obtained from the ether extract in alkaline side, but 2,3-dihydroxy-pyridine presumed was not obtained.

### Summary

(1) By heating furfural or furfural diacetate and ammonium sulfate in an autoclave at  $150\sim 155^{\circ}\text{C}$  for 3 hrs, 3-hydroxy-pyridine was obtained.

By similarly heating the above mentioned with hydroxylamine-hydrochloride, 2,3-dihydroxy-pyridine was obtained.

(2) By similar procedure, the intermediate of 5-nitro-furfural diacetate or diethoxy-dihydrofurfural diethylacetal and ammonium sulfate gave 2,3-dihydroxy-pyridine, but xylouronic acid did not give the desired pyridine derivatives. The formation of 2,3-dihydroxy-pyridine from the intermediate seems to depend on the differential structure of this starting material.

(3) By heating 5-nitro-furfural diacetate or 5-nitro-furfural and ammonium sulfate, succinic acid, fumaric acid and a colorless crystal melting at  $105\sim 110^{\circ}\text{C}$  were obtained, but pyridine derivatives were not obtained.

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