# Formation of 2-Methyl-3,6-dihydroxy-pyridine from Furyl methylketone and Hydroxylamine hydrochloride

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By

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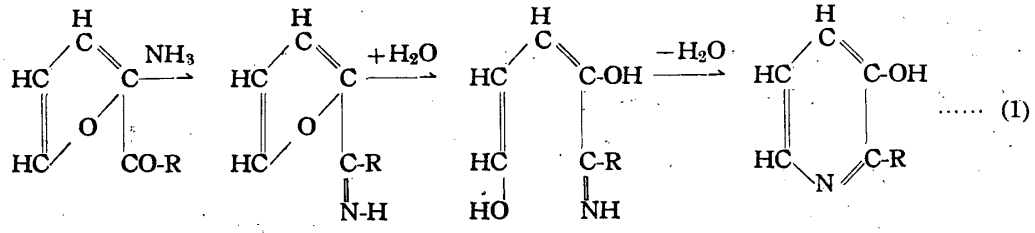
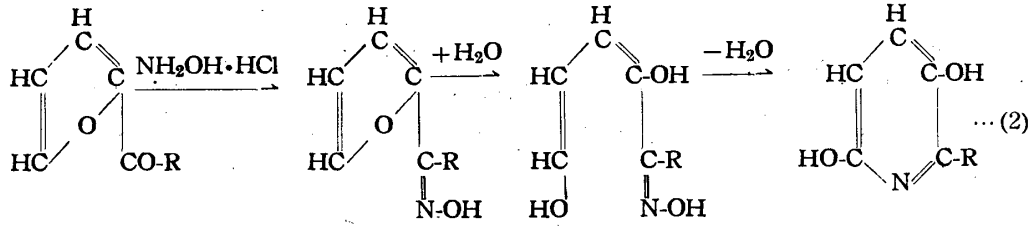
The former reports have already revealed[1)-7)] that $\beta$-hydroxy pyridine derivatives were formed from furan derivatives having carbonyl group in $\alpha$-position by heating with ammonium salts in autoclave, and the following formula was presented.




..... (1)

On the idea that 2,5-dihydroxy pyridine derivatives would be obtained by reacting as the following formula, furfural and hydroxylamine hydrochloride, instead of ammonium salts, were reacted.

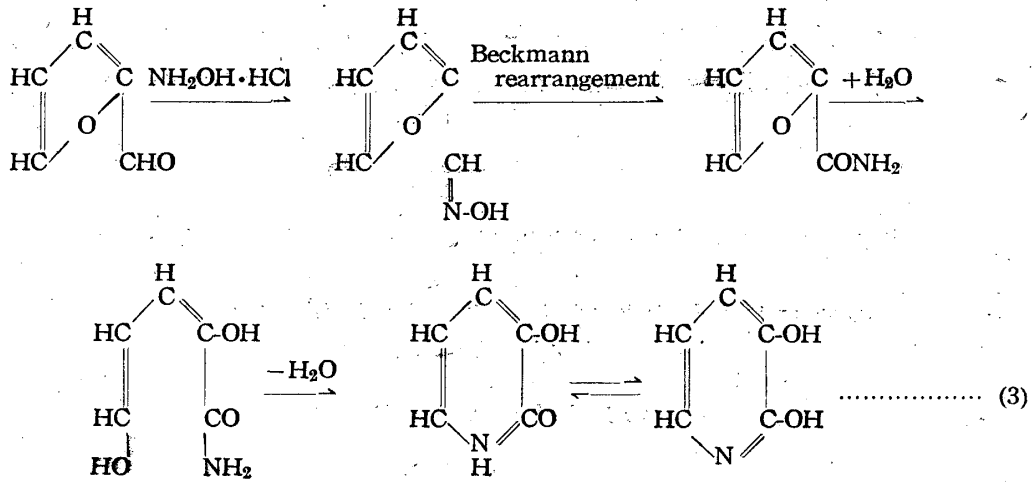



... (2)

Thus obtained crystals showed exactly the same property of 2,5-dihydroxy-pyridine described in *Beilstein's "Handbuch der organischen Chemie"*[8)].

But afterwards it baceame clear that 2,5-dihydroxy-pyridine described by *Beilstein* was mistaken, and in fact, it was 2,3-dihydroxy-pyridine[6),9),10)].

From this fact and the results of another experiment using pyromucic amide, the above formula was collected as follows:




..... (3)

Namely, furfuraloxime changed into pyromucic amide by Beckmann rearrangement and from pyromucic amide derived 2,3-dihydroxy-pyridine.

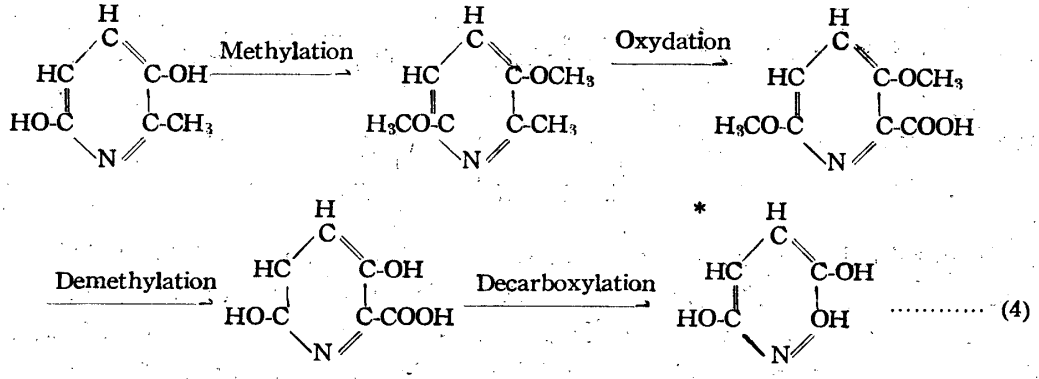
But when R in formula (2) is not H, the reaction may take the course shown in formula (2).

On this idea, furyl methylketone, instead of furfural, was reacted with hydroxylamine hydrochloride, and colorless needles having a formula corresponding to $C_6H_7O_2N$ were obtained.

This substance melts at 243~245°C (decomposes) and indicates a deep reddish violet color by $FeCl_3$ solution.

Oxime of furyl methylketone has also a formula corresponding to $C_6H_7O_2N$, but the melting point of the oxime is 104°C, and this shows no color by $FeCl_3$.

2-Methyl-3,6-dihydroxy-pyridine is not hitherto descrided in literature and the followlng experiments are now in progress to identify this substance.




..... (4)

* 2,5-Dihydroxy-pyridine was rescently synthesized by Hertog et al[11].

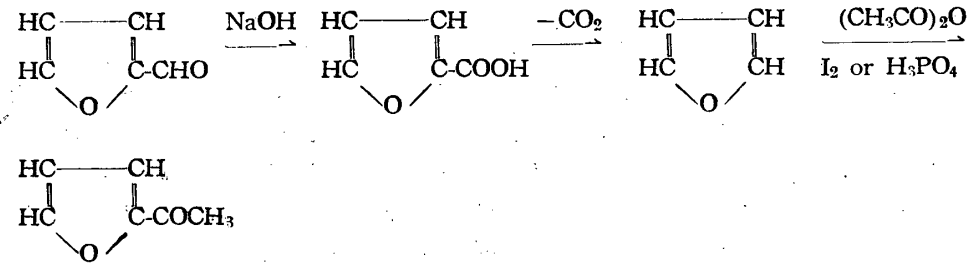
Though this substance is not yet identified, the authors believe it to be 2-methyl-3,6-dihydroxy-pyridine from the properties described above.

## Experimental

*Furyl methylketone*

Furyl methylketone was prepared by acetylation of furan which was prepared from pyromucic acid according to the method described in Gilman's *"Organic synthesis"* .

As the katalyst of acetylation $I_2$[13] or $H_3PO_4$[14] was used.




1) Synthesis using $I_2$ as katalyst[13].

Furan 10g, acetic anhydride 32g and $I_2$ 0.3g were heated slowly with stirring to 35°C in 30 minutes, then more rapidly to 60°C in next 30 minutes and the temperature was kept at 60°C for 30 minutes.

After cooling, 200ml water was added to the mixture, extracted with ether, and the extract was washed first with $Na_2CO_3$ then with $Na_2S_2O_3$ solution and finally dried over anhydrous $Na_2SO_4$. After removal of the solvent, the residue was distilled under reduced pressure, yielding 5.7g furyl methylketone. $b.p._{10}$ 60~65°C, m.p. 32°C. Oxime; colorless needle, m.p. 104°C.

2) Synthesis using $H_3PO_4$ as katalyst[14].

Furyl methylketone was prepared nearly in the same procedure using 85% $H_3PO_4$ instead of $I_2$. By this method the yield of furyl methylketone was higher than the former. Namely, 29.1g furyl methylketone was obtained from 34g furan, 100g acetic anhydride and 5g 85% $H_3PO_4$.

*2-Methyl-3,6-dihydroxy-pyridine*

Furyl methylketone 5.7g, hydroxylamine hydrochloride 4.4g and water 50ml were heated in autoclave at 155~160°C for 2 hours.

After cooling, the solution was filtered, concentrated to about half of the original volume under reduced pressure, alkalified with $Na_2CO_3$ and extracted with ether. After removal of the solvent, the residue was extracted with hot ligroin containing a little amount of ethanol. After cooling 0.1g yellow crystalls were obtained. After recrystallization from ethanol by the aid of charcoal, it was a colorless needle, m.p. 243~245°C, soluble in water, and the water solution indicates a deep reddish violet color by $FeCl_3$ solution.

Microanalysis.

| Sample (mg) | $CO_2$ (mg) | $H_2O$ (mg) | C% | H% |
|---|---|---|---|---|
| 1.383 | 2.927 | 0.692 | 57.72 | 5.60 |
| Theoretical | $C_6H_7O_2N$ | | 57·59 | 5.63 |
| Sample (mg) | N (cc) | b (mm) | t (°C) | N% |
| 3.984 | 0.373 | 762 | 15 | 10.90 |
| Theoretical | $C_6H_7O_2N$ | | | 11.19 |

Acetyl derivative

This substance 0.3 g, fused sodium acetate 0.5 g and acetic anhydride 2ml were heated at 150°C under reflux for 6.5 hours.

After removal of residual acetic anhydride under reduced pressure, the residue was extracted with 3 portions of 20ml ether, and the extract was washed with $Na_2CO_3$ solution and finally dried over anhydrous $Na_2SO_4$. After removal of the solvent, 0.45g. crude crystalls were obtained, m.p. 78°C. After being purified by sublimation under reduced pressure and recrystallization from dilute ethanol, it was a colorless plate, m.p. 80°C, soluble in alcohol, benzene and ether, nearly insoluble in cold water.

Alcohol solution of this crystal showed no color reaction by $FeCl_3$, but after being allowed to stand over night it showed a red color.

Microanalysis.

| Sample (mg) | $CO_2$ (mg) | $H_2O$ (mg) | C% | H% |
|---|---|---|---|---|
| 3.054 | 6.370 | 1.437 | 56.90 | 5.26 |
| Theoretical | $C_{10}H_{11}O_4N$ | | 57.41 | 5.30 |
| | $C_8H_9O_3N$ | | 57.04 | 5.42 |
| Sample (mg) | N (cc) | b (mm) | t (°C) | N% |
| 2.112 | 0.110 | 765 | 14 | 6.10 |
| Theoretical | $C_{10}H_{11}O_4N$ | | | 6.69 |
| | $C_8H_9O_3N$ | | | 8.37 |

## Summary

1) 2-Methyl-3, 6-dihydroxy-pyridine was synthesized by heating furyl methylketone and hydroxylamine hydrochloride in autoclave.

2) Furyl methylketone used in this experiment was prepared by acetylating furan with acetic anhydride using $I_2$ or $H_3PO_4$ as the katalyst.

Acknowledgement

We express our deep gratitude to Dr. Teiichi Tamura for his kind supply of large quantity of furfural which we used as the raw material of this experiment, and also to the micro analyzer of the department of agricultural chemistry, faculty of agriculture, Tokyo University.

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