

REACTION OF FURAN DERIVATIVES WITH AMMONIA VII THE REACTION MECHANISM OF FURAN DERIVATIVES WITH AMMONIA

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α -pyrrylketones was not mentioned. Dunlop (8) reported that 2-acetylpyrrole only was produced from 2-acetylfuran with ammonia in the absence of any solvent, moreover he proposed other formation mechanism.

However, I have found it possible to obtain β -hydroxy-pyridines and α -pyrrylketones by reacting α -furylketones with ammonia under the same condition as mentioned previously (6, 7, 8, 9), and have thought that the reaction of α -furylketones with ammonia is different from the reaction mechanism described above.

This investigation has been carried out to prove the reaction mechanism of α -furylketones with ammonia, on the basis of this work, it seemed reasonable to assume that β -hydroxy-pyridines and α -pyrrylketones have been formed according to the reaction mechanism as shown in the following.

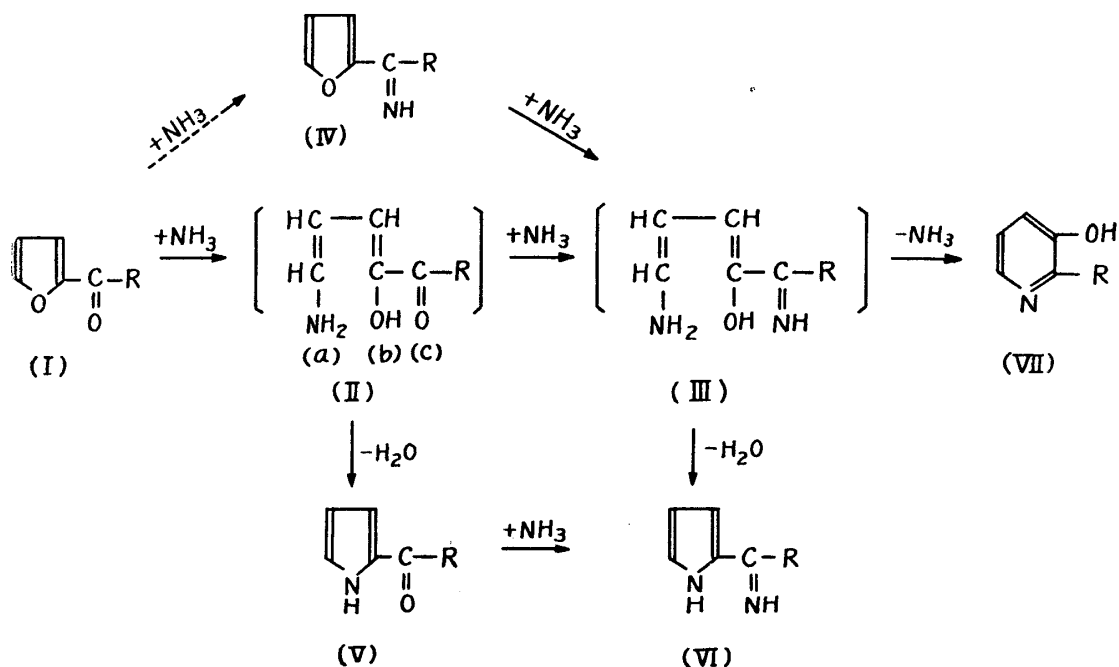


Fig. 1. The reaction mechanism of α -furylketones with ammonia.

Experimental

A) Reaction of 2-acetylfuran with ammonia at room temperature.

1) 2-Acetylfuran 5 g, NH_4OH 50 ml, methanol 50 ml and NH_4Cl 0.5 g were reacted in the pressure-tube at 15°C for a week, after removal of the solvent and ammonia at reduced pressure, the residue was dried over CaCl_2 , and then it was distilled under reduced pressure, yielding 4.8 g of 2-acetylfuran, bp_{10} $60\sim 65^\circ\text{C}$, m.p. 32°C . 2,4-Dinitro-phenylhydrazone of this substance, m.p. $218\sim 220^\circ\text{C}$, was identical with that of 2-acetylfuran.

2) 2-Acetylfuran 5 g, liquid ammonia 20 ml and NH_4Cl 0.5 g were reacted

in the same condition as described above. After treating by the same procedure mentioned above, the residue was distilled under reduced pressure, yielding 4.6 g of 2-acetylfuran, bp₁₀ 60~65°C.

B) Reaction in several conditions.

1) 2-Acetylfuran 2 g, liquid ammonia 10 ml, methanol 10 ml and NH₄Cl 0.2 g were heated in an autoclave at several temperatures as shown in Table 1 for 5 hr, the reaction mixture was diluted with 50 ml of methanol, and treated with active carbon. After removal of the solvent and ammonia at reduced pressure, the residue was dried over CaCl₂. The reaction products were separated from dried material by the method of sublimation at reduced pressure. The yield of 2-methyl-3-hydroxy-pyridine and 2-acetylpyrrole is shown in the following Table 1.

Table 1. The reaction products in several conditions (1).

°C	Reaction product g	Loss by adsorption to charcoal g	2-Methyl-3-hydroxy pyridine g	2-Acetylpyrrole g
100	1.35	0.15	—	0.32
120	1.40	0.30	—	0.40
130	1.60	0.20	0.21	0.41
150	1.75	0.15	0.51	0.46
180	1.95	0.20	0.60	0.54
220	1.60	0.40	0.60	0.54

C) Analysis of the reaction product by paper partition chromatographic method in the application of ultra-violet spectrum.

1) The standard solution for the analysis was prepared as follows, 2-methyl-3-hydroxy-pyridine 60 mg, 45 mg, 30 mg, 15 mg and 7.5 mg respectively were dissolved in 25 ml of methanol, and then 25 ml of methanol solution containing 30 mg, 22.5 mg, 15 mg, 7.5 mg and 3.75 mg respectively were prepared as the standard solution. The 1/100 ml of each solution was spotted on filter paper (Toyo No. 51). After irrigating the chromatogram with *n*-butanol: acetic acid: water (v/v 4:1:5), the chromatogram was lighted by an ultra-violet lamp, the spots which

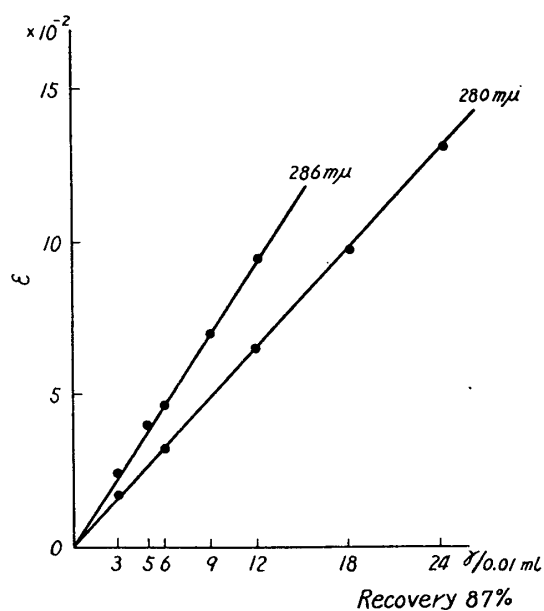


Fig. 2. The standard curve for the analysis of the reaction products.

are emitting fluorescence were detected in R_f 0.55 and R_f 0.90. The spot in R_f 0.55 was that of 2-methyl-3-hydroxy-pyridine, R_f 0.90, 2-acetylpyrrole; each spot was extracted with 5 ml of methanol, and then methanol solution was measured at the absorption in 280, 286 $m\mu$ by the ultra-violet spectrophotometer. In this work, wave length 280 $m\mu$ was used to analyse 2-methyl-3-hydroxy-pyridine, 286 $m\mu$ to 2-acetylpyrrole. The results are shown in Fig. 2.

2) 2-Acetylfuran 1 g, liquid ammonia 5 ml, methanol 5 ml and NH_4Cl 0.1 g were heated in an autoclave at 180°C in the several conditions as shown in Fig. 3, the reaction mixture was diluted with 10 ml of methanol, and treated with active carbon, moreover methanol solution was filled up to 250 ml with methanol. And then 0.01 ml of methanol solution was spotted on filter paper, and methanol solution containing the reaction products was submitted to paper

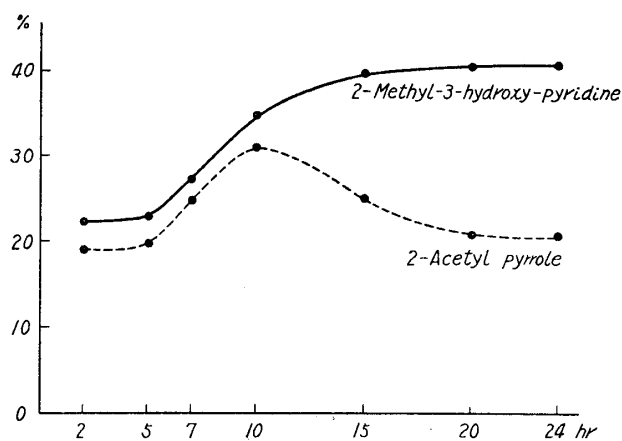


Fig. 3. The reaction products in several conditions (2).

partition chromatography as shown above, 2-methyl-3-hydroxy-pyridine and 2-acetylpyrrole were quantitatively determined according to the above standard curve by measuring the absorption of methanol extract. The results are shown in Fig. 3. D) Reaction of 2-acetylfuran with ammonia (1 mole : 1 mole).

1) 2-Acetylfuran 5g and 10 ml of methanol containing

liquid ammonia 1.3 ml (0.78 g) were heated in an autoclave at 100°C for 2 hr, 100 ml of methanol was added to the reaction mixture, and it was treated with active carbon. After removal of the solvent under reduced pressure, the residue was distilled under reduced pressure, yielding 2.5 g of 2-acetylfuran, bp_{10} 60~65°C, and then 2-acetylpyrrole 0.1 g was distilled at bp_{10} 95~100°C. The residue distilled was extracted with 2N-NaOH, and NaOH solution was saturated with CO_2 and then extracted again with ether for 48 hr, but nothing was obtained from ether extract. Also the reaction product was recognized to be a mixture of 2-acetylfuran and 2-acetylpyrrole by the application of paper partition chromatography.

2) 2-Acetylfuran 3 g and 25 ml of methanol containing liquid ammonia 0.8 ml (0.48 g) were heated in an autoclave at 180°C for 20 hr, the reaction mixture was diluted with 25 ml of methanol and treated with active carbon. After removal of the solvent at reduced pressure, the residue was taken up with ether. Ether solution was extracted with 2N-NaOH to isolate phenolic

substance, 0.5 g of 2-acetylpyrrole remained in the ether solution, and NaOH solution was saturated with CO_2 and then extracted again with ether for 48 hr. The syrupy extract indicated a red color by FeCl_3 solution, a green color by Folin-Denis reagent, but 2-methyl-3-hydroxy-pyridine presumed was not obtained.

E) Reaction in several conditions at 100°C .

1) 2-Acetylfuran 2 g, liquid ammonia 10 ml and NH_4Cl 0.5 g were heated in an autoclave at 100°C for 2 hr, after removal of ammonia, the residue was distilled under reduced pressure, yielding 0.7 g of 2-acetylfuran, bp_{10} $60\sim 65^\circ\text{C}$, and then $2\sim 4$ g of 2-acetylpyrrole was distilled at bp_{10} $95\sim 100^\circ\text{C}$. The distilled residue was extracted with 2N-NaOH, and NaOH solution was saturated with CO_2 and then extracted with ether for 48 hr, but β -hydroxy-pyridine derivative was not obtained from the ether extract. Also 2-acetylfuran, alcoholic ammonia and NH_4Cl were heated in the same condition described above, but main portion of the products was 2-acetylpyrrole, and other was 2-acetylfuran, the starting material.

2) 2-Acetylfuran 2 g, liquid ammonia 15 ml and NH_4Cl 0.5 g were heated in an autoclave at 100°C for 10 hr, after removal of ammonia, 50 ml of methanol was added to the reaction mixture, and then treated with active carbon. After removal of the solvent under reduced pressure, the residue was distilled under reduced pressure, 2-acetylpyrrole 0.5 g was distilled at bp_{10} $95\sim 100^\circ\text{C}$. The distilled residue was extracted with 2N-NaOH, NaOH solution was saturated with CO_2 , and then extracted with ether for 48 hr, but β -hydroxy-pyridine derivative was not obtained. Moreover, the reaction product was detected to be 2-acetylpyrrole only by the application of paper partition chromatographic method.

F) Syntheses of 2-furyl-methylketimine and 2-furyl-phenylketimine.

1) 2-Furyl-methylketimine: In a 200 ml flask fitted with a magnetic stirrer, 50 ml dropping funnel and a reflux condenser to which is attached a CaCl_2 -tube, were placed 0.64 g of magnesium turnings, a small crystal of iodine and a portion of ether solution (10 ml contains 3.8 g of methyl iodide). Stirring was started, as soon as the reaction was started, the main portion of ether solution containing methyl iodide was added, the solution was refluxed gently for 1.5 hr to complete the reaction. The water-bath was removed, the flask was cooled to $0\sim 5^\circ\text{C}$, and furfuronitrile 2.5 g in 10 ml of dry ether was added slowly during 20 min, the mixture was refluxed with stirring for 2 hr. The reaction mixture was cooled and ether was removed by decantation, and washed with dry ether. Crushed ice and NH_4Cl were added to the reaction mixture to decompose the Grignard compound. The mixture was extracted with ether, the ether extract was dried over anhydrous Na_2SO_4 , and then saturated with dry hydrochloride. After cooling over night, 2-furyl-methyl-

ketimine hydrochloride was precipitated in crystalline, yield 0.7 g, m.p. 78~79°C. This crude product was recrystallized from methanol and ethylacetate, slight yellow needle, m.p. 83~85°C. This substance indicated a milky yellow color by Mayer reagent. Anal. Found: C, 44.17; H, 6.09; N, 8.94, Calcd. $C_6H_7NO \cdot HCl \cdot H_2O$: C, 44.01; H, 6.13; N, 8.59 per cent. The infrared spectrum of 2-furylmethylketimine hydrochloride monohydrate is shown in Fig. 4.

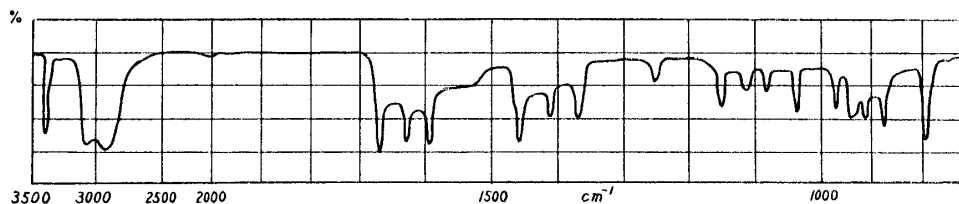


Fig. 4. The infrared spectrum of 2-furyl-methylketimine-hydrochloride.

2) 2-Furyl-phenylketimine: 2-Furyl-phenylketimine 15 ml hydrochloride was prepared from brom-benzene 7.0 g in 20 ml of dry ether and furfuronitrile 4.6 g in 20 ml of dry ether by the same procedure described above, yielding 3.0 g. This substance was recrystallized from methanol and ethyl acetate, a colorless prism, m.p. 226~228°C, and indicated a deep milky yellow color by Mayer reagent. Anal. Found: C, 63.59; H, 4.85; N, 6.87 per cent. Calcd. $C_{11}H_9NO \cdot HCl$: C, 63.45; H, 4.73; N, 6.63 per cent. The infrared spectrum of 2-furyl-phenylketimine hydrochloride is shown in Fig. 5.

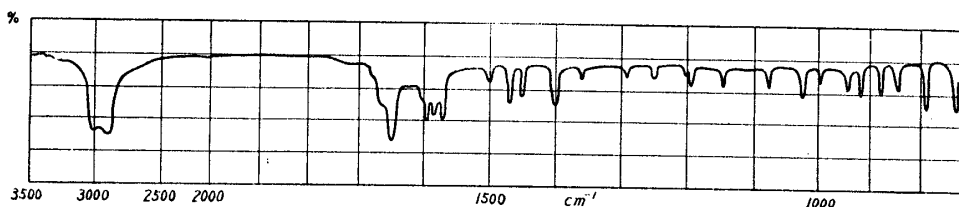


Fig. 5. The infrared spectrum of 2-furyl-phenylketimine-hydrochloride.

G) *Reaction of α -furylketimines with ammonia.*

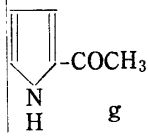
1) 2-Furyl-methylketimine hydrochloride 0.2g, liquid ammonia 15ml were heated in an autoclave at 180°C for 20 hr, the reaction mixture was diluted with 20 ml of methanol, and treated with active carbon. After removal of the solvent under reduced pressure, the residue was dried over $CaCl_2$. The reaction product was separated from dried material by sublimation at reduced pressure, 0.12g of 2-methyl-3-hydroxy-pyridine was obtained, but 2-acetylpyrrole was not obtained. Using a portion of the reaction mixture, two spots of R_f 0.55 and R_f 0.40 were detected by paper partition chromatographic method. The spot of R_f 0.55 was 2-methyl-3-hydroxy-pyridine, other spot of R_f 0.40 was that of 2-methylpyrrolketimine as mentioned in the following.

2) 2-Furyl-phenylketimine hydrochloride 0.5 g and liquid ammonia 5 ml were heated in an autoclave at 180°C for 15 hrs., the reaction mixture was diluted with 20 ml of methanol, and treated with active carbon. After removal of the solvent under reduced pressure, the residue was taken up with ether. Ether solution was extracted with 2N-NaOH to isolate 2-phenyl-3-hydroxy-pyridine, and NaOH solution was saturated with CO₂ and then extracted again with ether for 48 hr. The three tenth g of 2-phenyl-3-hydroxy-pyridine was obtained from ether extract, m.p. 202°C, but 2-phenyl-pyrrylketone was not obtained as the reaction product.

H) Reaction of 2-acetylpyrrole with ammonia.

The reactants as shown in Table 2 were heated in an autoclave at 180°C for 10~20hr, the reaction mixture was diluted with 20 ml of methanol, and treated with active carbon. After removal of the solvent at reduced pressure, the residue was dried over CaCl₂, the reaction products were separated from dried material by the application of sublimation under reduced pressure. As shown in Table 2, the main portion of the obtained product was 2-acetylpyrrole which was unchanged in this reaction, and the other was detected to be a substance of *R_f* 0.40 by paper partition chromatography. From the above results, it was recognized that 2-acetylpyrrole was not converted into 2-methyl-3-hydroxy-pyridine in this reaction.

Table 2. The reaction products of 2-acetylpyrrole with ammonia.

	Temp. °C	Hour hr	Raw products g	Sub- limed g	Residue g	 g	<i>R_f</i> 0.40 g
2-Acetylpyrrole 0.2 g Liq. NH ₃ 5 ml MeOH 5 ml	180	10	0.18	0.13	0.05	0.11	0.02
2-Acetylpyrrole 0.2 g Liq. NH ₃ 10 ml NH ₄ Cl trace	180	10	0.19	0.15	0.04	0.12	0.03
2-Acetylpyrrole 0.2 g 28% NH ₄ OH 10 ml MeOH 10 ml	180	10	0.20	0.16	0.04	0.11	0.05
2-Acetylpyrrole 0.2 g Liq. NH ₃ 5 ml MeOH 5 ml NH ₄ Cl trace	180	20	0.20	0.15	0.05	0.10	0.05

I) 2-Methylpyrrylketimine.

A segment of the spot *R_f* 0.40 in paper partition chromatogram was extracted with 5 ml of methanol, and then methanol extract was measured at the absorption in wave length 220~320 mμ. The ultra-violet spectrum of the above extract is shown in Fig. 6. λ_{max} 243 mμ, 292~295 mμ, λ_{min} 260 mμ. When the spectrum of this substance was compared with that of 2-acetylpyrrole, the former was similar to that of 2-acetylpyrrole, but the absorption

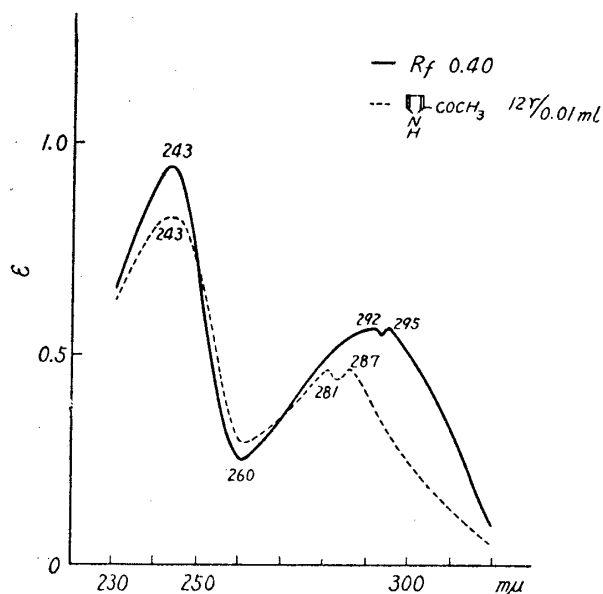


Fig. 6. The ultra-violet spectrum of R_f 0.40-extract. (MeOH)

band caused a shift of λ_{\max} to longer wave lengths. From the facts described previously (10, 11), it was supposed that the segment corresponding to R_f 0.40 might be 2-methyl-pyrrylketimine (2-acetylpyrrole-imine) formed according to the reaction mechanism as shown in Fig. 2.

Summary

Various kinds of β -hydroxypyridines and α -pyrrylketones were obtained by the reaction of α -furylketones with ammonia, but their formation mechanism was uncertain. This investiga-

tion was carried out to prove the reaction mechanism of α -furylketones with ammonia. From the results, it seemed reasonable to assume that β -hydroxypyridines and α -pyrrylketones have been formed according to the reaction mechanism as shown in Fig. 1.

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