STUDIES ON THE AUTOCLAVED PRODUCTS OF POLYURONIDES

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By

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[I] Introduction

In 1930, I began to study the chemical constitution of alginic acid under Dr. Teijiro Yabuta's guidance and obtained a colorless needle by heating alginic acid (polymannuronide) with water in an autoclave and also the same crystal similarly from pectin (polygalacturonide) and gummic acid (polyglucuronide). The crystal melted at 235°C (all the following temperature degree is Centigrade), gave a violet color by $FeCl_3$ and had the formula $C_{10}H_8O_4$. The crystal constitution was found to be 2-methyl-3,8-dihydroxy-chromone (I) and this was named "Alginetin"[1] and presumed its formation mechanism.[4]
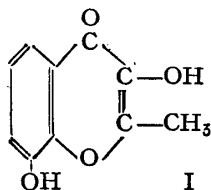

By heating 2-hydroxy-3,ω-dimethoxy-acetophenone obtained from I with benzoic anhydride and anhydrous sodium benzoate, 3,8-dimethoxy-flavone was synthesized.[5]

5-Hydroxymethyl-furfural-ether was obtained[2] similarly by heating hexoses instead of polyuronides with water in an autoclave, and bis-(5-hydroxymethyl-furfur-acrylic acid)-ether was synthesized[3] by application of the Perkin reaction on the ether.

By heating a chlorine-bleached brown algae "Konbu" (*Laminaria*) with water in an autoclave for the purpose to simplify the preparation of I, a rhombic crystal melting at 208° was obtained.[11] It was strong acidic and had a strong reduction power; its formula was $C_5H_6O_3$.

During my study on its chemical constitution, Reichstein and Oppenauer[17] also obtained the same crystal from uronic acid by heating with H_2SO_4 under pressure and showed it to be 2-cyclo-pentane-2,3-diol-1-on (II) and named it "Reductic acid".

$$\begin{array}{cc} OH & OH \\ | & | \\ C &\!\!=\!\! C \\ | & | \\ H_2C & CO \\ & \diagdown C \diagup \\ & H_2 \end{array} \quad II$$
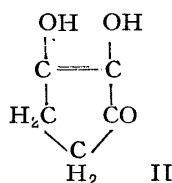
I studied the derivatives of II and proposed its presumed mechanism of formation.[6]

Next, when "Konbu" was autoclaved with a dilute H_2SO_4 solution for the purpose of simpler preparation of II, a white prism melting at $127°$ and having a formula C_5H_5NO was obtained[11] with II.

It was evidenced that it was 3-hydroxy-pyridine (III) by its properties and synthesis, and formed by reaction of furfural converted from alginic acid in "Konbu" and ammonia derived from nitrogen compounds in the algae.

$$\left\langle \!\!\!\!\!\! \bigcirc \!\!\!\!\!\! \right\rangle \!\!-\!\! OH$$
$$N \qquad III$$
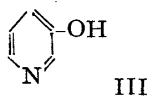
By development of this formation mechanism of III, the following β-hydroxy-pyridines were obtained

(1) 5-Methyl-furfural $+(NH_4)_2SO_4$ →2-Methyl-5-hydroxy-pyridine[14]

(2) Furylmethylketon $+(NH_4)_2SO_4$ →2-Methyl-3-hydroxy-pyridine[15]

(3) Furfural $+NH_2OHHCl$ →2,3-Dihydroxy-pyridine[12)10]

(4) Furfural $+NH_2NH_2H_2SO_4$ →3-Hydroxy-pyridine+
                                  2,3-Dihdroxy-pyridine[10)13]

(5) 5-Methylfurfural $+NH_2OHHCl$ →2-Methyl-5,6-dihydroxy-pyridine[10]

(6) Furylmethylketone $+NH_2OHHCl$ →2-Methyl-3,6-dihydroxy-pyridine[16]

(7) Pentose $+(NH_4)_2SO_4$ →3-Hydroxy-pyridine[16]

(8) Pentose $+NH_2OHHCl$ →3-Hydroxy-pyridine+
                              2,3-Dihydroxy-pyridine[10]

(9) Hexose $+(NH_4)_2SO_4$ ⎰2-Hydroxymethyl-5-hydroxy-pyridine
                              ⎨2-Methyl-5-hydroxy-pyridine
                              ⎩2-Methyl-5,6-dihydroxy-pyridine[8)9)10]

(10) Hexose $+NH_2OHHCl$ →Levulinic acid+Succinic acid[10]

Since the above reports were mainly written before the Second World-War and separately, I now make a comprehensive paper of the 16 reports with a hope

of new development. It is desired that the readers refer to the original reports for details.

[II] Formation of Alginetin from Polyuronides and Synthesis of 3,8-Dimethoxy-flavone

(A) Formation of Alginetin[1]

A colorless needle (from water) melting at 235° was obtained by heating alginic acid with water at 155~160° for 3 hours in an autoclave, concentrating its hot filtrate in vacuo and extracting the concentrate with ether. Its yields were 1~3 per cent and it was also obtained similarly from HCl- and H_2O-washed brown algaes (yields 0.5~1.0 per cent), from fruit pectin (1~2 per cent), and from gummic acid (0.6 per cent).

The crystal was little soluble in cold water, benzene and ligroin, but easily soluble in warm ethanol. Its water solution was neutral to litmus paper and gave a violet color by $FeCl_3$ and its formula was $C_{10}H_8O_4$. The acetate was a white needle melting at 125° and the benzoate was a colorless needle melting at 187°.

Since β-methyl-daphnetin (IV) according to literature has the same formula $C_{10}H_8O_4$ having two hydroxy radicals and melting at the same temperature but its $FeCl_3$ reaction is green, the above crystal showed a depression of 15° on the results of mixed melting with IV synthesized from pyrogallol and aceto-acetic ester by the Peckmann and Duisberg method.[18]
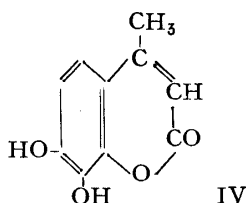
Therefore, I named it "Alginetin" as a new substance.

(B) The Chemical Constitution of Alginetin[1]

2,3-Dihydroxy-benzoic acid (V) by H_2O_2-oxidation of I, V+pyrocatechine (VI)+acetic acid by alkali fusion of I, and then, mono methyl-ether (VII) and dimethyl-ether (VIII) by methylation of I with diazomethane or dimethylsulfate were obtained. VII was a white needle, m.p. 215° and gave a violet color by $FeCl_3$ and the acetate was a white needle, m.p. 171°. VIII was a white needle, m.p. 105°. VII and VIII were oxidised to 2-hydroxy-3-methoxy-benzoic acid (IX) (a needle, m.p. 148°,) by H_2O_2.

Though I and VII were difficult to decompose by alkali, a white needle (X) melting at 66° and acetic acid were obtained by easy alkali decomposition of VIII.

The crystal (X) was little soluble in cold water, but easily soluble in ethanol and benzene, and gave a dark green color by $FeCl_3$ and had the formula $C_{10}H_{12}O_4$ having two methoxy radicals and gave a mono-oxime (a white prism, m.p. 121°), and gave IX by its alkali decomposition. Inversely, by heating X with acetic anhydride and anhydrous sodium-acetate on the oil bath, VIII was synthesized. From the above facts, it was cleared that X was 2-hydroxy-3,ω-dimethoxy-acetophenone and, I, VII and VIII were, therefore, respectively 2-methyl-3,8-dihydroxy-chromone, 2-methyl-3-methoxy-chromone and 2-methyl-3,8-dimethoxy-chromone.

By hydrogenation of the dimethyl ether (VIII) with platinum black, two
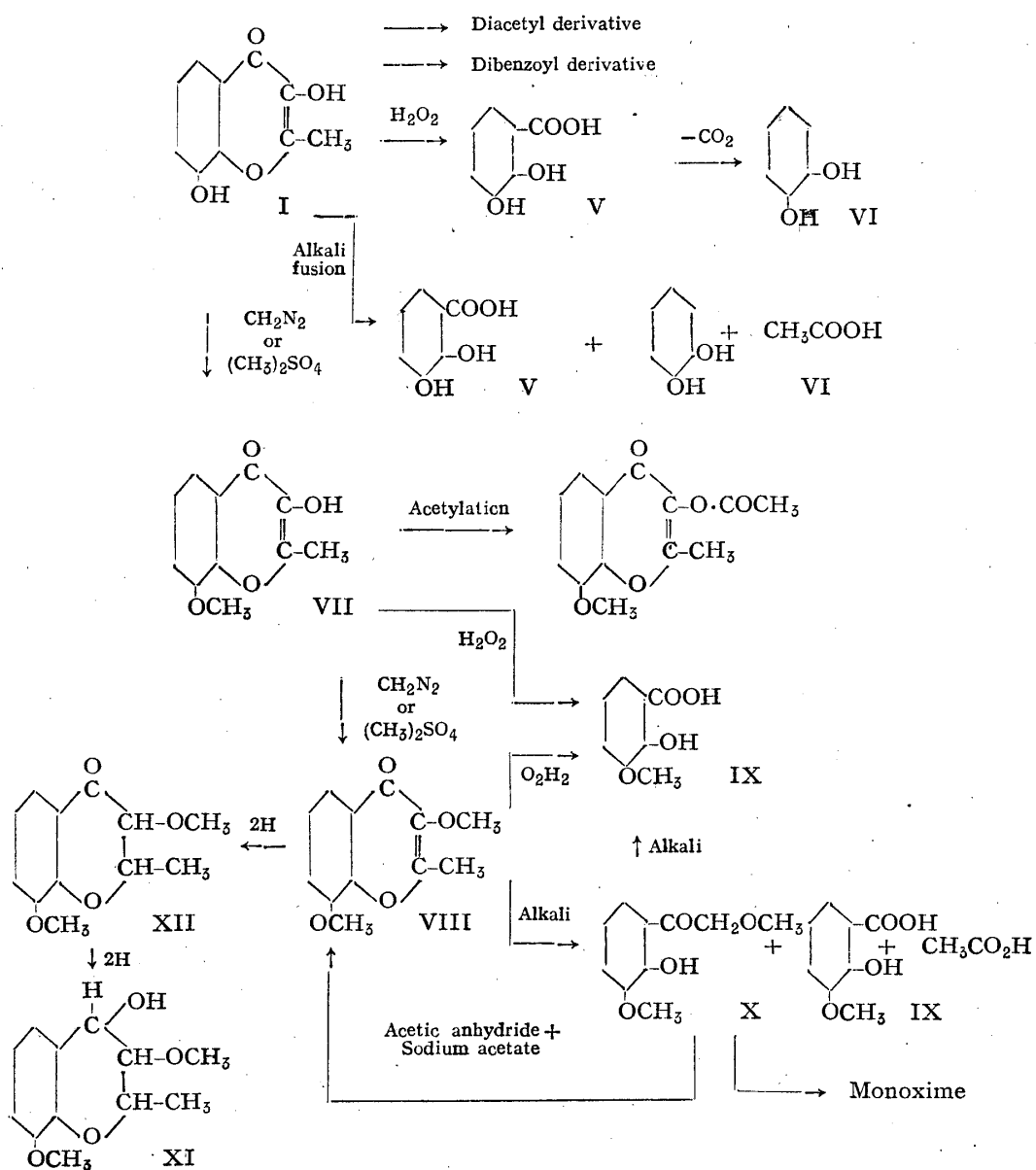
Fig. 1.   Shows those Chemical Constitutions.

white needles melting at 182° and 95° were obtained. The former (XI) had the formula $C_{12}H_{16}O_4$ corresponding to tetrahydro-derivative of VIII and gave a mono-acetyl derivative (a colorless prism, m.p. 117°). It was presumed that XI would be 2-methyl-3,8-dimethoxy-4-hydroxy-chromone and the latter (XII) would be perphaps 2-methyl-3,8-dimethoxy-2,3-dihydro-chromone.

(C)Formation Mechanism of Alginetin

Since alginetin (I) was also obtained with reductic acid (II) by heating polyuronides in an autoclave as described later, I proposed[7] the next presumed equation by thinking a deep relation between the formation of the both crystals.
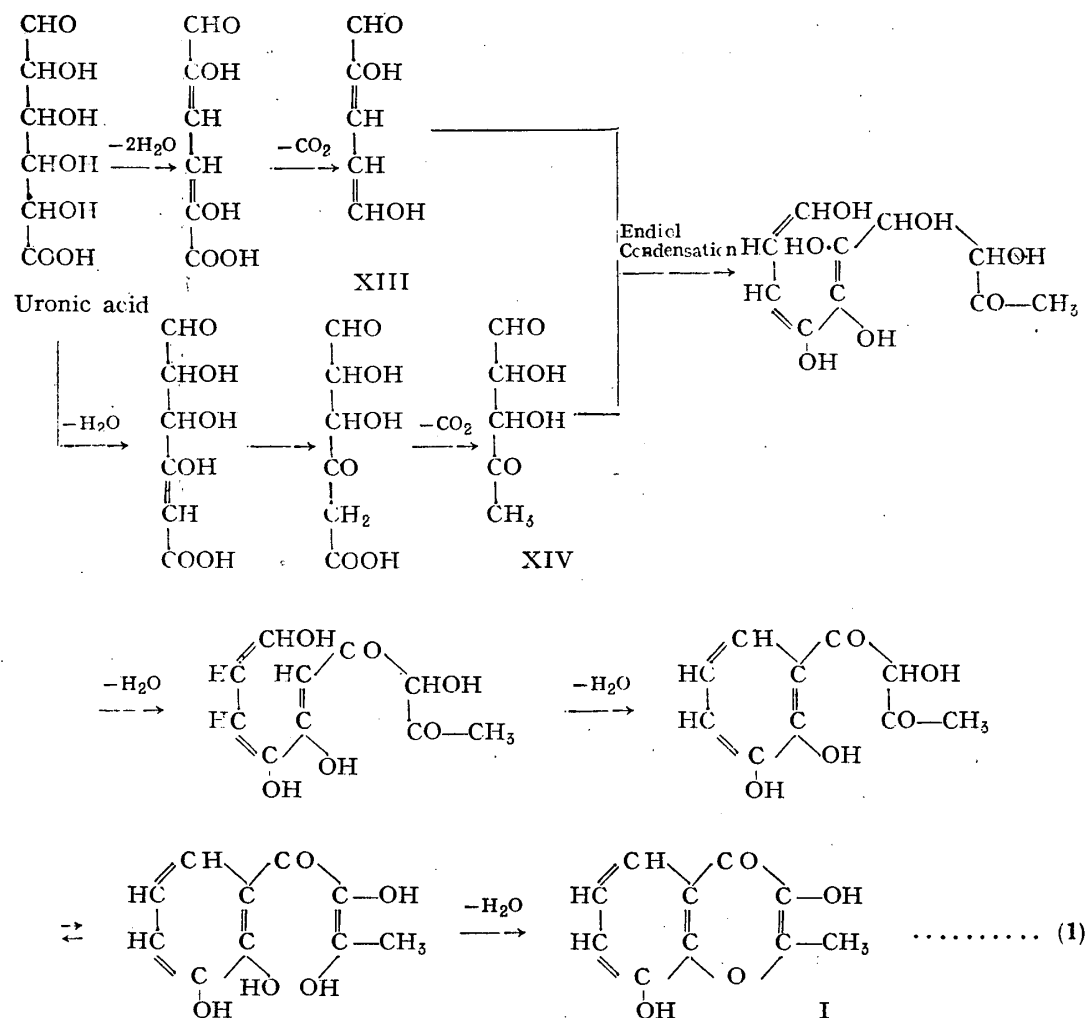
After the report was published, I now think dihydroxyacetone (XV) and acetic acid than XIV as the intermediate and wish to propose the next equation that I would be formed from the two and 2,4-pentadiene-2,5-triol-1-al (XIII).

$$\text{(2)}$$
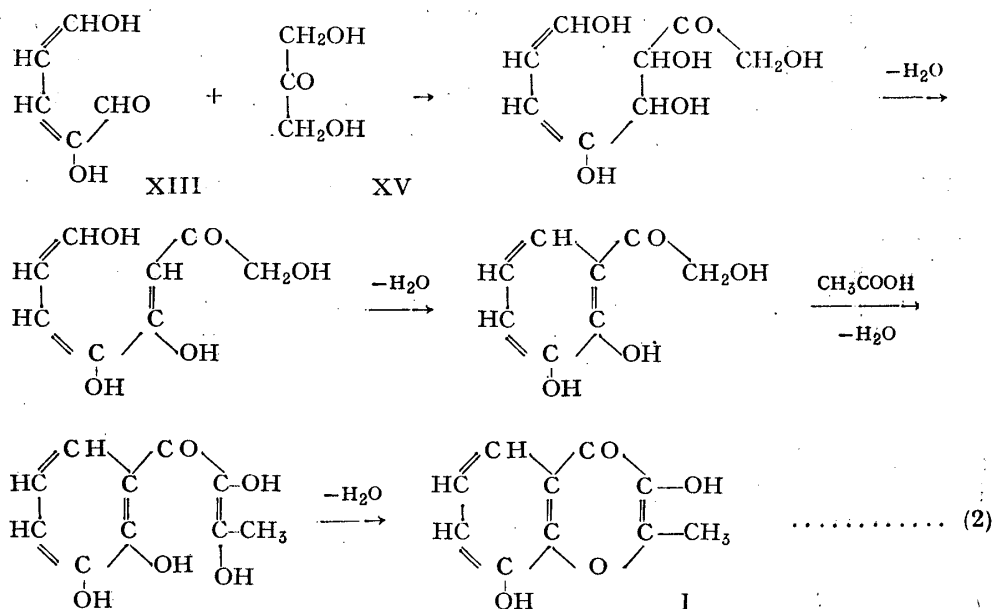
(D) Synthesis of 3,8-Dimethoxy-flavone[1]

A yellow prism melting at 156–7° was obtained by using benzoic anhydride and anhydrous sodium benzoate in place of acetic anhydride and anhydrous sodium acetate as synthesis of I from 2-hydroxy-3,ω-dimethoxy-acetpohenone (X).

It had a formula $C_{17}H_{14}O_4$ and was little soluble in water and easily soluble in warm ethanol and gave no color by $FeCl_3$ and no reductic reaction with Mg and HCl. Two maximum of its absorption spectrum were on wave length'/3320 and 3920 and the spectrum was similar to that of flavones. From the above facts, the yellow crystal should be 3,8-dimethoxy-flavone (XVI).
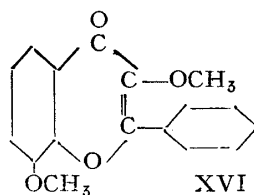
[III] Formation of 5-Hydroxymethyl-furfural-ether from Hexoses and Synthesis of Bis-(5-hydroxymethyl-furfur-acrylic-acid)-ether

(A) Formation of 5-Hydroxymethyl-furfural-ether

A white plate melting at 112° was obtained[2] by similar treating glucose, fructose, sucrose, starch and agar as the formation of alginetin from polyuronides.

Its yields were 1~2 per cent and its formula was $C_{12}H_{10}O_5$ and the hydrazone was a plate melting at 145°. A mixture of this crystal with the authentic samples of 5-hydroxymethyl-furfural-ether (XVII) synthesized by the Feulgen and Imhäuser method[19] showed no depression of melting point. It might be probably produced by dehydration of two molecules of 5-hydroxymethyl-furfural (XVIII) converted from hexose.

$$2 \quad HO\text{-}H_2C\text{—}\underset{\displaystyle XVIII}{\underset{\displaystyle O}{\overset{\displaystyle HC\text{——}CH}{C \qquad C}}}\text{—CHO} \quad \xrightarrow{-H_2O} \quad OHC\text{—}\underset{\displaystyle O}{\overset{\displaystyle HC\text{——}CH}{C \qquad C}}\text{—CH}_2\text{-O-CH}_2\text{—}\underset{\displaystyle XVII}{\underset{\displaystyle O}{\overset{\displaystyle HC\text{——}CH}{C \qquad C}}}\text{—CHO} \quad .. \quad (3)$$
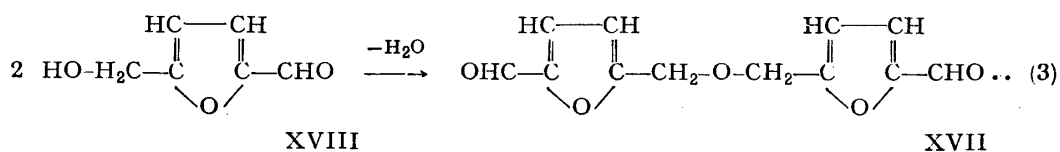
(B) Synthesis of Bis-(5-hydroxymethyl-furfur-acrylic-acid)-ether (XX)

By heating the above ether (XVII) with acetic anhydride and anhydrous sodium acetate as the synthesis of furfur-acrylic acid (XIX) from furfural by the Perkin reaction, a white plate melting at 203–4° was obtained. It was little soluble in water, ligroin and cold ethanol, but soluble in hot ethanol and acetone. It was acidic to a litmus paper and did not reduced the Fehling solution and had the formula $C_{16}H_{14}O_7$.

$$\underset{\displaystyle XIX}{\underset{\displaystyle O}{\overset{\displaystyle HC\text{——}CH}{HC \qquad C}}}\text{—CH=CH-COOH} \quad , \qquad \left(HOOC\text{-HC=HC—}\underset{\displaystyle O}{\overset{\displaystyle HC\text{——}CH}{C \qquad C}}\text{—CH}_2\text{-} \right)_2 O \quad XX$$
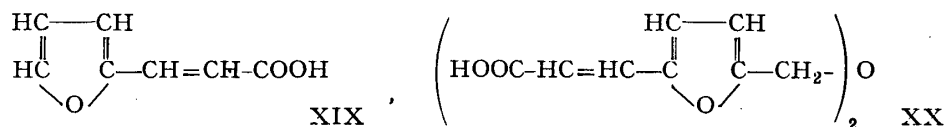
On the exprimental results of antiseptic activity of XVII and XX for soy, XVII showed no antiseptic power below 0.1 per cent concentration and XX had almost no antiseptic power compared to the strong activity of XIX.

[IV] Formation of Reductic Acid from Polyuronides

During the investigation of alginetin (I), a strong acidic substance melting at 208° and having a strong reduction power was obtained with I by heating a chlorine-bleached and water-washed "Konbu" with water in an autoclave. However, in the course of study of its chemical constitution, Reichstein and Oppenauer[17] obtained the same crystal (m.p. 213° (correct)) by decomposing uronic acid with H_2SO_4 and showed it to be 2-cyclopentene-2,3-diol-1-on (II) and named it "Reductic àcid"

Below is an outline of my report[6] relating to reductic acid :

(A) Formation of Reductic acid

Table 1 shows the decomposing conditions and yields of I and II. I used the next two methods with respect to isolation of I and II from the decomposed solution.

(i) By concentrating the warm decomposed filtrate in vacuo, extracting it with ethylether using the Soxlet, removing the solvent, dissolving the residue in a little ethanol and cooling it in a refrigerator, I at first crystalised out and then, II was obtained by cooling its filtrate added with ether.

(ii) The H_2SO_4 decomposed filtrate was neutralized with lime and then, lead acetate solution was added to its filtrate. The lead salts obtained was washed with water and decomposed by H_2S or H_2SO_4 and then, by concentrating its filtrate in vacuo, the crystal of II was obtained.

Table 1.

Material (g)	H_2O or H_2SO_4 sol. (ml)	Temp. (°C)	Time (hr)	I (g)	II (g)	Treating method
"Konbu" (bleached by Cl_2 gas) 100	H_2O 4,000	160	3	0.15	0.13	(i)
"Konbu" (1% HCl and H_2O-washed) 850	H_2O 3,000 contained conc H_2SO_4 100	155–160	2.5	—	17.50	(ii)
Alginic acid 10	2% H_2SO_4 500	160	2	—	0.60	(i)
Fruit pectin 100	H_2O 4.000	160	3	0.33	0.40	(i)
Gummic acid 10	5% H_2SO_4 50	150–155	1.5	—	0.1	(i)
Furfural 50	conc H_2SO_4 10 H_2O 100	160–17	2	—	0.20	(i)

(B) The Properties and Derivatives of II

II was a colorless rhombic prism (from water) that melted at 208° (decomp.)

Its water solution was acidic to Congo red paper and reduced Fehling solution and 2,6-dichlorophenol-indophenol, and gave a twinkle violet color by $FeCl_3$ in the presence of sodium acetate. The anilide was a yellow needle, m.p. 197° (decomp.). By reacting with phenylhydrazine-hyrochlcride, II gave at first a reddish brown needle that melted at 246–7° and next a yellowish-brown plate that melted at 208° by the reaction with more phenylhydrazine-hydrochloride.

Reichstein and Oppenauer found that the former was the di-phenylhydrazone of cyclopentane-1,2,3-triketone (XXI) and the latter was the tri-phenylhydrazone of XXI.

$$
\begin{array}{c}
\text{CO——CO} \\
| \quad\quad | \\
\text{CH}_2 \ \text{CO} \\
\diagdown \diagup \\
\text{CH}_2 \quad \text{XXI}
\end{array}
$$
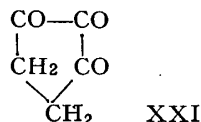
Similarly, when the oxime of II was prepared, the trioxime of XXI was obtained. It was a white plate decomposing at 198–9°. Cyclopentane-1,2-diol (XXII) was obtained by hydrogenation of II with Ni-catalyst under hydrogen pressure. It was a colorless crystalized mass, melting at ca. 30° and boiling at 117∼120°/9mm, and its bis-phenylurethane was a colorless needle that melted at 207°.

$$
\begin{array}{c}
\text{CH}_2\text{——CH——OH} \\
| \quad\quad | \\
\text{CH}_2 \ \text{CH——OH} \\
\diagdown \diagup \\
\text{CH}_2 \quad \text{XXII}
\end{array}
$$
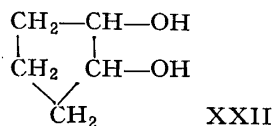
By CH_2N_2-methylation of II, monomethylether (XXIII) and dimethylether (XXIV) were obtained. XXIII was a colorless prism melting at 130∼131° and its water solution was neutral to a litmus paper and gave a blue color by $FeCl_3$.

XXIV was a colorless liquid boiling at 117∼8°/12mm and gave no color by $FeCl_3$. By alkali decomposing of XXIV, another monomethylether (XXV) was obtained and also, the same crystal was obtained by methylation of II with dimethylsulfate. It was a colorless prism melting at 134° and its water solution was acidic to a Congo red paper and gave a twinkle violet color by $FeCl_3$ and reduced neither Fehling solution nor 2,6-dichloro-phenol-indophenol.

It showed a monobasic acid by titration with N/10 NaOH and gave a barium salt which was a colorless prism (from 60% ethanol), and also para-Br-phenacyl-ester that melted at 91–2°. Reichstein et al reported XXIII to be 2-cyclo-pentene-3-methoxy-2-ol-1-on but did not report on the other methylether (XXV). Since XXV showed strong acidic properties as tetronic acid and hydroresorcinol having the radical (-C(OH)=CH-CO-) and gave a trihydrazone and a trioxime of the triketone (XXI), it should be 2-cyclo-pentene-2-methoxy-3-ol-1-on.
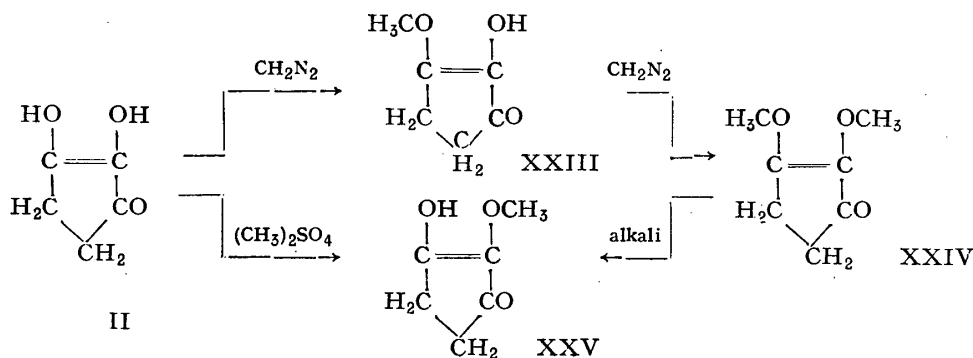
Previously, I named[3] "Reductic acid methyl ether" and "Methyl-reductic acid" respectively for XXIII and XXV. Recently, Hesse and Böckmann[20] named "Methyl-reductic acid" for one of the decompsed products of calotropine which was a cardiac poison in Africa, and would have a constitution of 5-methyl-1,3-cyclo-pentadiene-1,2,3-triol (XXVI).

$$HO—C \!=\! C—OH$$
$$\underset{H_3C—CH}{|} \quad \underset{C—OH}{|}$$
$$\underset{CH}{\diagdown\!\diagup} \quad XXVI$$
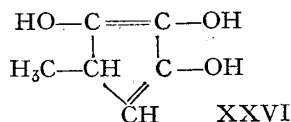
Therefore, to remove confusion, I now change the names of XXIII and XXV respectively to "Reductic-acid-3-methyl-ether" and "-2-methyl-ether." When XXV was oxidised by $AgCO_3$ in its water solution or by $KMnO_4$ in its acidic solution, a white prism melting at 183° (decomp.) was obtained. It was neutral and thus there was no $FeCl_3$ reaction or sodium nitropruside reaction, aud its formula was $C_{10}H_8O_4(OCH_3)_2$; it was named temporarily "Reductic-acid-2-methyl-ether-oxide" (XXVII) which previously[6] was named "Methyl-reductic-acid-oxide." By boiling the oxide with dilute HCl solution, about a half of the original amount was obtained as XXV and, by boiling it with alcoholic potassium, a white needle decomposing at 253~250°, being acidic and having a formula $C_{10}H_7O_4(OCH_3)$ was obtained.

From the above experiments, it was supposed that the oxide would have the following constitution.

$$H_3CO—C \!=\! C—O—C——C—OCH_3$$

XXVII
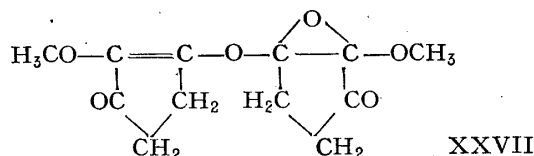
(C) Formation Mechanism of Reductic acid

From the facts that II was obtained from furfural (see Table 1), and methyl-glyoxal acetic acid ($OHC\text{-}CO\text{-}CH_2\text{-}CH_2\text{-}COOH$) from uronic acid,[21] and levulinic aldehyde ($OHC\text{-}CH_2CH_2\text{-}CO\text{-}CH_3$) from 2-methyl-furan[22] and etc., I proposed the next course (4) in which II would be produced by forming α-keto-glutar-aldehyde (XXVIII) as an intermediate form from uronic acid and then its place would be taken by endiol-condensation.

$$
\begin{array}{ccc}
\begin{array}{c}
\mathrm{CH_2{-}CH_2} \\
\mid \quad\;\; \mid \\
\mathrm{CHO} \;\; \mathrm{CO} \\
\mid \\
\mathrm{CHO} \\
\mathrm{XXVIII}
\end{array}
& \rightarrow &
\begin{array}{c}
\mathrm{CH_2{-}CH_2} \\
\mid \quad\;\; \mid \\
\mathrm{C} \qquad \mathrm{CO} \\
\diagup\;\diagdown\!\mathrm{C}\diagup \\
\mathrm{OH}\;\;\; \mid \\
\mathrm{OH} \quad \mathrm{II}
\end{array}
\end{array}
\qquad\qquad \cdots\cdots\cdots\cdots\cdots (4)
$$
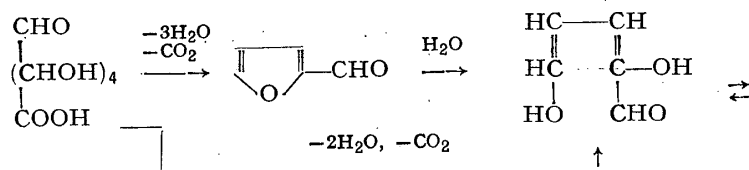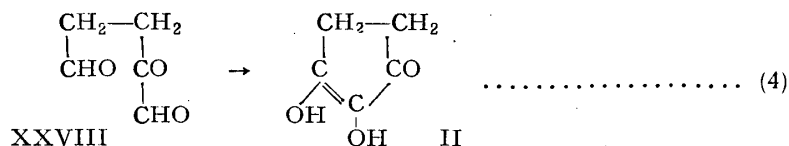
Since the formation of XXVIII through furfural was doubtful and II was produced more difficultly from furfural than from polyuronides (Dutch patent[25] obtained also a small yield of II from furfural), I adopted the formation mechanism not through furfural in the above course. Recently, Wolfrom et al.[24] reported a new formation mechanism of furfural (XXX) passing through XXIX on the following equation.

$$
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{CHOH} \\
\mid \qquad -\mathrm{H_2O} \\
\mathrm{CHOH} \;\; \xrightarrow{\quad\quad} \\
\mid \\
\mathrm{CHOH} \\
\mid \\
\mathrm{CH_2OH} \quad -\mathrm{H_2O}
\end{array}
\quad
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{C{-}OH} \\
\parallel \\
\mathrm{CH} \quad \rightleftarrows \\
\mid \\
\mathrm{CHOH} \\
\mid \\
\cdot \mathrm{CH_2OH}
\end{array}
\quad
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{CO} \\
\mid \qquad -\mathrm{H_2O} \\
\mathrm{CH_2} \;\; \xrightarrow{\quad\quad} \\
\mid \\
\mathrm{CHOH} \\
\mid \\
\mathrm{CH_2OH}
\end{array}
\quad
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{CO} \\
\mid \\
\mathrm{CH} \\
\parallel \\
\mathrm{CH} \\
\mid \\
\mathrm{CH_2OH}
\end{array}
$$

$$
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{C} \\
\parallel \qquad\quad \\
\mathrm{CH} \qquad \mathrm{O} \\
\mid \\
\mathrm{CHOH} \\
\mid \\
\mathrm{CH_2}
\end{array}
\;
\begin{array}{c}
-\mathrm{H_2O} \\
\xrightarrow{\quad\quad}
\end{array}
\;
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{HC{=}C} \diagdown \\
\mid \qquad \mathrm{O} \\
\mathrm{HC{=}C}\diagup \\
\diagdown \mathrm{H}
\end{array}
\;
\begin{array}{c}
-\mathrm{H_2O} \\
\xleftarrow{\quad\quad}
\end{array}
\;
\begin{array}{c}
\mathrm{CHO} \\
\mid \\
\mathrm{HC{-}C{-}OH} \\
\parallel \qquad\; \diagdown\mathrm{O} \\
\mathrm{HC{-}C}\diagdown \mathrm{H} \\
\mid \\
\mathrm{H}
\end{array}
\; \leftarrow
\qquad \cdots\cdots\cdots (5)
$$

XXXI XXX XXIX
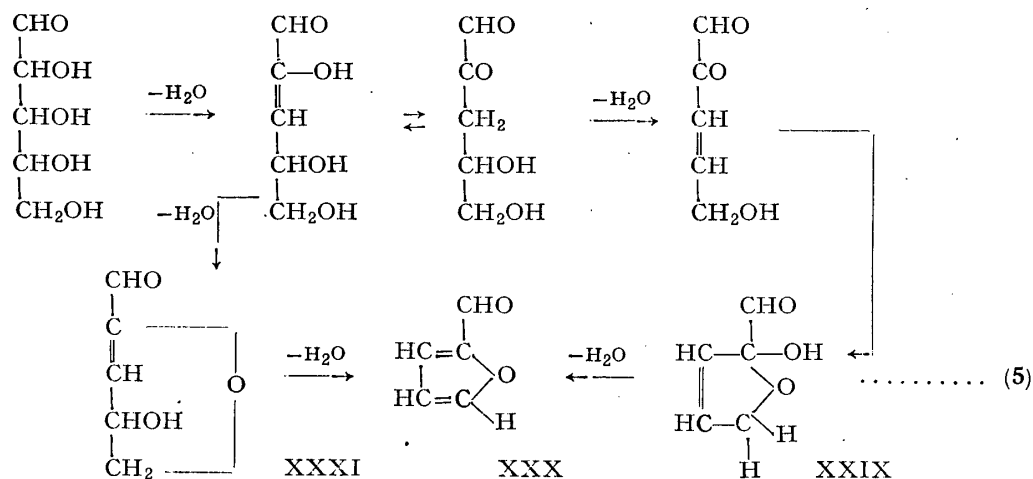
However, the mechanism of Hurd and Isenhour[25] passing through XXXI was hitherto generally recognized. From this new theory, it is supposed that II would be produced from α-keto-glutaraldehyde (XXVIII) probably obtained by oppening of the furan nucleus of XXIX. After my article it was reported that II was produced by acid hydrolysis of wood[26] and by acid decomposition of pectin,[27] and synthesized by three differential methods.[28][29][30].

[V] Formation of 3-Hydroxy-pyridine from Polyuronides, Pentose or Furfural and Ammonium salts[11]

(A) 3-Hydroxy-pyridine from "Konbu"

For the purpose of simple yet sufficient preparation of reductic acid, a dil. HCl and then H_2O washed brown algae "Konbu" was decomposed by heating with dil. H_2SO_4 in an autoclave and neutralized with lime, and reductic acid was precipitated as Pb-salt by the addition of lead acetate to its filtrate. When the Pb-removed solution by passing H_2S gas in the filtrate was concentrated in vacuo and extracted with ether, a white prism melting at 127° was obtained.

It had a formula C_5H_5NO and was easily soluble in water and ethanol, and its water solution was alkalic to a litmus paper and gave a red color by $FeCl_3$. Its picrate was a yellow long needle, m.p. $201\sim2°$ and the oxalate was a colorless prism, m.p. $178\sim9°$. Those properties were similar to that of 3-hydroxy-pyridine (III) and the melting point of the crystal was undepressed on an admixture with authentic III synthesized by the Murmann method.[31]

(B) Formation Mechanism of 3-Hydroxy-pyridine

Dr. T. Yabuta suggested to me that, since N-phenyl-3-hydroxy-pyridine (XXXII) was a derivative of III and was obtained from furfural (XXX) and aniline-hydrogenchloride as shown in the following, III would be produced similarly from furfural which was converted from alginic acid in the algae and ammonium-salts which was formed from nitrogen compounds in the algae.

$$\cdots \cdots \cdots \cdots \cdots \cdots \cdots (6)$$

Therefore, at first by heating furfural with ammonium sulfate in an autoclave, III was obtained, and next by heating alginic acid with ammonium sulfate in a dil. H_2SO_4 solution in an autoclave, III and reductic acid were obtained. Also, III was obtained by using ammonium-chloride, ammonium-oxalate, ammonium-acetate and urea in place of ammonium sulfate, and from furfuramide (XXXIII) only, and from xylose and ammonium sulfate.

Table 2 shows the conditions of formation and yields of III and II.

From the above, the following several mechanisms of formation of III were thought.

i) At fitst, III would be produced as in the above described course (6):

$$\text{(furfural structure)} \xrightarrow[-H_2O]{\cdot 2NH_3} \text{(aminovinyl structure)} \xrightarrow{-NH_3} \text{(3-hydroxypyridine) III} \qquad \cdots\cdots\cdots (7)$$

Table 2.

	Temp. (°C)	Time (hr)	3-Hydroxy-pyridine (g)	Reductic acid (g)
Laminaria 850 g, H_2SO_4 100g, Water 2.5 *l*	155～160	2.5	1.7	17.5
Ecklonis bicyclis 2 kg, H_2SO_4 200g, Water 6 L	〃	〃	2.7	36.0
Alginic acid 10 g, $(NH_4)_2SO_4$ 10 g, H_2SO_4 10 g, Water 100 ml	〃	2	0.2	0.3
Xylose 14 g, NH_4Cl 10 g, Water 100 ml	〃	〃	0.2	—
Xylose 10 g, $(NH_4)_2SO_4$ 10 g, Water 100 ml	128～133	〃	0.1	—
Furfural 20 g, $(NH_4)_2SO_4$ 20 g, Water 200 ml	155～160	〃	2.0	—
F. 20 g, $(NH_4)_2SO_4$ 30 g, Water 100 ml	132～135	〃	0.4	—
F. 20 g, $(NH_4)_2SO_4$ 50 g, Water 200 ml	100	15	—	—
F. 20 g, $(NH_4)_2SO_4$ 20 g, Water 200 ml Alcohol 50 ml	125	2	0.3	—
F. 20 g, $(NH_4)_2SO_4$ 20 g, Water 200 ml Alcohol 50 ml	145	〃	0.8	—
F. 20 g, NH_4Cl 16 g, Water 200 ml Alcohol 50 ml	125	〃	0.1	—
F. 20 g, NH_4Cl 16 g, Water 200 ml Alcohol 50 ml	145	〃	0.2	—
F. 20 g, NH_4Cl 25 g, 1 : 3 HCl 200 ml	100	5	0.08	—
F. 20 g, Urea 20 g, Water 200 ml	150	2	1.0	—
F. 20 g, Ammonium oxalate 26 g, Water 200 ml	152～155	〃	1.0	—
F. 20 g, Ammonium acetate 57 g, Water 200 ml	〃	〃	0.5	—
Furfuramide 10 g, Water 100 ml	155～160	〃	0.2	—
Furfuramide 15 g, H_2SO_4 6 g, Water 150 ml	〃	〃	0.5	—

(F. = Furfural)

Foreign investigators adopted mainly this mechanism, and recently, Ledit-schke[33] also adopted it in his report of synthesis of 3-hydroxy-2-phenyl-pyridines (XXXV), in which he heated phenyl-α-furyl-ketone (XXXIV) with ammonium salts in an autoclave.

$$\cdots\cdots (8)$$
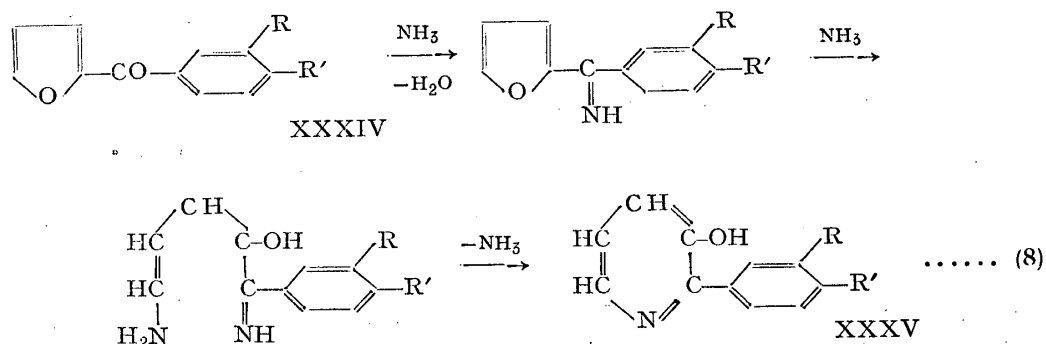
ii)   From the similar case of formation of reductic acid and III, III would be formed by reacting ammonium salt on 2,4-pentadiene-2,5-diol-1-al (XXXVI) which was previously[3] thought as an intermediate of the formation of reductic acid from polyuronides.

$$\cdots\cdots (9)$$
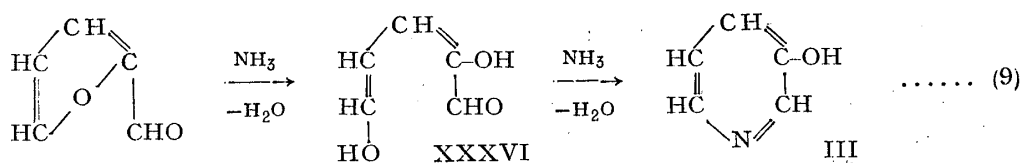
iii)   From the fact that pyrol was produced by heating furan with NH_3 in an autoclave, III would be produced as shown in the next equation :

$$\cdots\cdots\cdots\cdots\cdots (10)$$
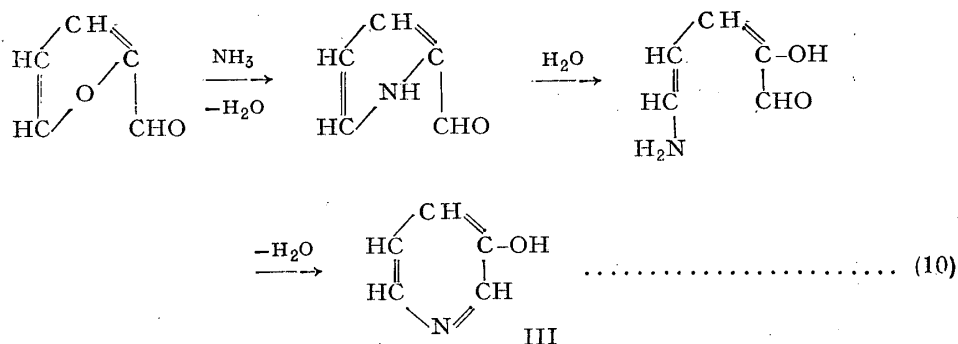
iv)   At first, furfur-imide (XXXVII) would be produced from furfural and NH_3, and next, III would be formed as shown in the next course :

$$
\begin{array}{ccc}
\overset{CH}{\underset{HC\diagdown_O\diagup C}{HC}}\overset{}{\underset{CHO}{}} & \xrightarrow[-H_2O]{NH_3} & \overset{CH}{\underset{HC\diagdown_O\diagup C}{HC}}\overset{}{\underset{\underset{NH}{CH}}{}} \xrightarrow{H_2O} & \overset{CH}{\underset{HC\diagup \diagdown CH}{HC}}\overset{C-OH}{\underset{OH \quad NH}{}}
\end{array}
$$

XXXVII

$$
\xrightarrow{-H_2O} \quad \overset{CH}{\underset{HC\diagup \underset{N}{\diagdown} CH}{HC}}\overset{C-OH}{\underset{}{}} \qquad \cdots\cdots\cdots\cdots\cdots (11)
$$

III
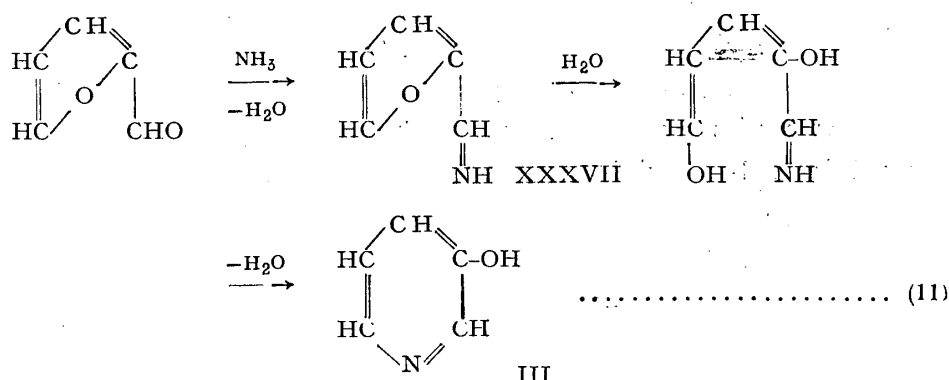
Though several courses of formation of III were thought as above mentioned, I adopted the last course (11) by attaching great importance to the formation of III from furfur-amide (XXXIII) only. Recently the chemical Abstracts (1951) reported that Rombaut and Smets[54] produced derivatives of β-hydroxy-pyridine having a supposed constitution of XXXVlll-a or XXXVlll-b by condensing one molecule of furfural with two of aniline.

$$
\begin{array}{cc}
OC\!-\!\!-\!CH & HC\!=\!\!=\!CH \\
| \quad \| & | \quad | \\
H_2C \quad CH & \text{or} \qquad H_2C \quad CO \\
| \quad | & | \quad | \\
H_5C_6\!-\!N\!-\!\!-\!CH\!-\!NH\!-\!C_6H_5 & H_5C_6\!-\!N\!-\!\!-\!CH\!-\!NH\!-\!C_6H_5 \\
\text{XXXVIII a} & \text{XXXVIII b}
\end{array}
$$

Though I was unable to see the original report, it may be thought as one course of its formation that it may have a constitution of XXXVlll-c formed as given in the following equation :

$$
\overset{}{\underset{O}{\boxed{}}}\!\!-\!CHO + 2\ C_6H_5NH_2 \xrightarrow{-H_2O} \overset{}{\underset{O}{\boxed{}}}\!\!-\!CH\!\!\diagup\overset{NH-C_6H_5}{\diagdown NH-C_6H_5} \xrightarrow{H_2O}
$$

$$
\begin{array}{ccc}
\overset{HC-CH}{\underset{HC \quad C\text{-}OH}{\Vert \quad \Vert}} & & \overset{HC-CH}{\underset{HC \quad C\text{-}OH}{\Vert \quad \Vert}} & & \overset{HC- CH_2}{\underset{HC \quad CO}{\Vert \quad |}} \\
| \quad | \diagup NH\text{-}C_6H_5 & \xrightarrow{-H_2O} & | \quad | & \rightleftarrows & | \quad | & \qquad \cdots (12) \\
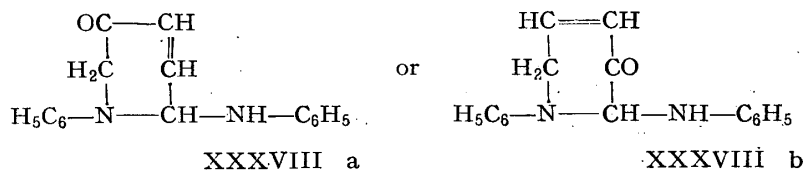HO \quad CH\diagdown NH\text{-}C_6H_5 & & H_5C_6\text{-}N\!-\!CH\text{-}NH\cdot C_6H_5 & & H_5C_6N\!-\!CH\text{-}NH\cdot C_6H_5
\end{array}
$$

XXXIIII c
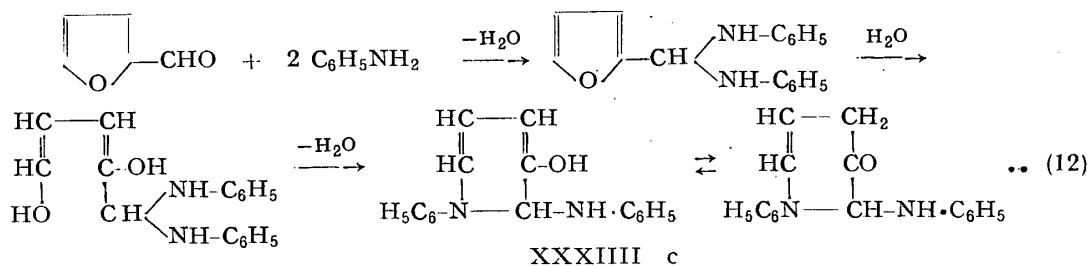
[VI] Formation of β-Hydroxy-pyridine Derivatives from 5-Methyl-furfural or Furyl-methylketone and Ammonium Salts.

(A) 2-Methyl-5-hydroxy-pyridine from 5-Methyl-furfural and $(NH_4)_2SO_4$.[14]

Similarly, by heating 5-methyl-furfural with $(NH_4)_2SO_4$ in an autoclave as the formation of 3-hydroxy-pyridine from furfural and $(NH_4)_2SO_4$, a colorless prism melting at 166-7° was obtained. Its formula was C_6H_7NO and its

water-solution was alkalic to a litums paper and gave a red color by $FeCl_3$. The picrate was a yellow long prism, m. p. 203~4° and the acetate was a color-less liquid, b. p. 113~4°/19 mm ; its picrate was a yellow needle, m. p. 146~7°. Those properties were similar to 2-methyl-5-hydroxy-pyridine (XXXIX) derived from 2-methyl-5-amino-pyridine by Graf.[35]
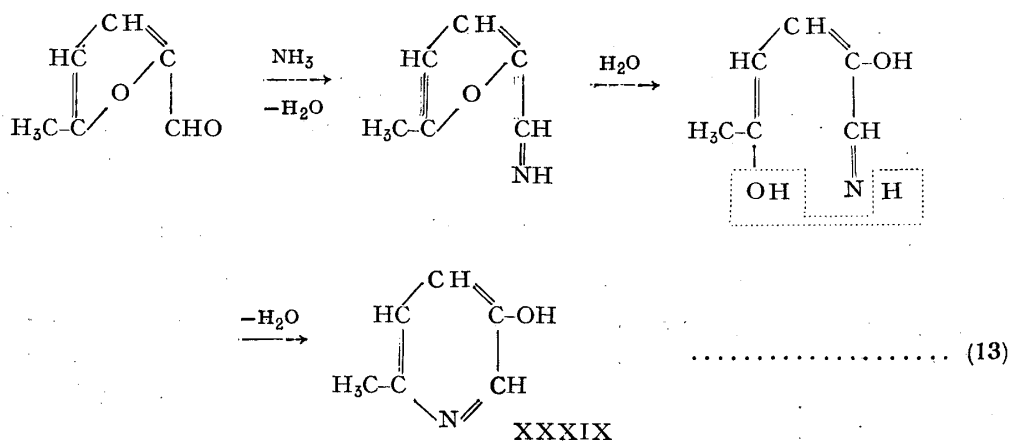

$$ \cdots\cdots\cdots\cdots\cdots (13) $$

(B) 2-Methyl-3-hydroxy-pyridine from Furylmethylketone and $(NH_4)_2SO_4$.[15]

By similarly heating furylmethylketone (XXXX) with $(NH_4)_2SO_4$ in an autoclave, a colorless prism melting at 167~8° was obtained. Its formula was C_6H_7NO and its water-solution gave a deep red color by $FeCl_3$ and the picrate was a yellow needle, m.p. 202~3° (decomp.). Since this crystal had the same formula and similar derivatives as the above described 2-methyl-5-hydroxy-pyridine, the results of mixed melting of both the bases and the picrate showed respectively depression of 11° and 12°.

The crystal was similar to 2-methyl-3-hydroxy-pyridine (XXXXI) reported by Dornow[36] (1940), which was synthesized in connection with Vitamin B_6 and was a colorless prism, m. p. 167~8° and gav ea deep red colorby $FeCl_3$ and its picrate melted at 204°.

Though the authentic sample of XXXXI was not synthesized, I presumed it to be XXXXI and to have been produced as shown in the following course.

$$ \cdots\cdots\cdots\cdots\cdots (14) $$
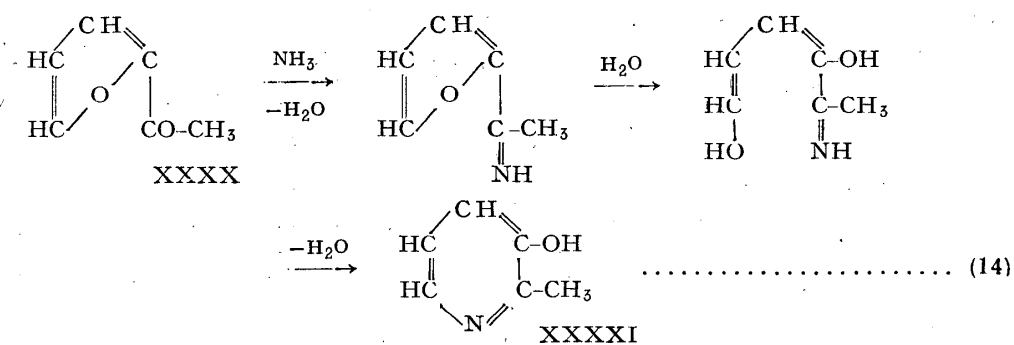
[VII] Formation of Dihydroxy-pyridine Derivatives from Furfural, 5-Methyl-furfural or Furyl-methyl-ketone and $NH_2OH \cdot HCl$ or $NH_2 \cdot NH_2 \cdot H_2SO_4$

(A) 2,3-Dihydroxy-pyridine from Furfural and $NH_2OH \cdot HCl$.[12)10)]

When a mixture of furfural 20g., $NH_2OH \cdot HCl$ 20g. and H_2O 200 ml. was heated at 155~160° for 2 hours in an autoclave and the reaction filtrate was concentrated in vacuo and extracted with ether after making it alkalic by the addition of Na_2CO_3, a crude crystal of 0.5 g. was obtained. It crystalized in colorless prisms from ethanol with charcoal and melted at 248°.

It gave a deep blue color by $FeCl_3$ and its formula was $C_5H_5NO_2$ and the mono-acetate was a colorless needle, m. p. 153°.

Its properties were similar to that of 2,5-dihydroxy-pyridine (XXXXII) described in the "Beilstein : Handbuch der Organischen Chemie" and the melting point of the crystal was undepressed on admixture with authentic sample synthesized by Kudernatsch method[37)].

Therefore, I first reported[12)] that the crystal would be produced as shown in the next course :

$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots (15)$$
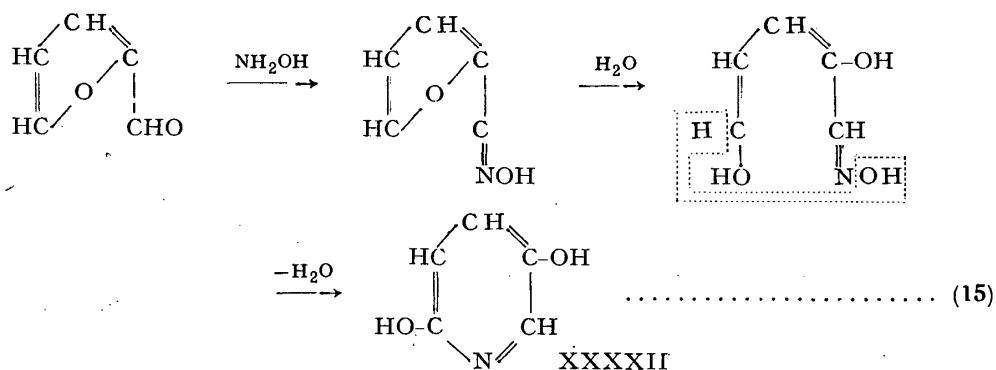
After the report, I found two correction reports of Schickl et al[38)] and Plazek et al[39)] in which it was stated that Kudernatsch's dihydroxy-pyridine was not 2,5-dihyroxy-pyridine (this crystal was recently synthesized by Hertog et al[40)]), but it was 2,3-dihydroxy-pyridine (XXXXIII).

Therefore, I thought that the corrected mechanism of formation of the crystal would be as shown in the next course involving pyromucic amide (XXXXIV) produced by Beckmann's rearrangement of furfural-oxime.

$$\text{(16)}$$
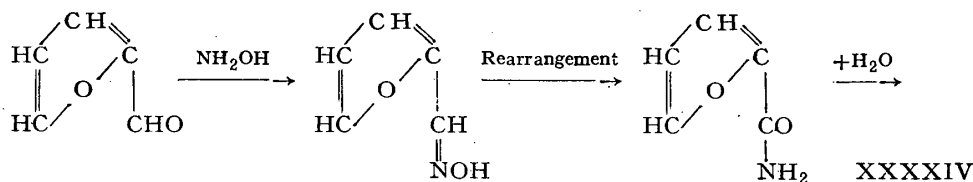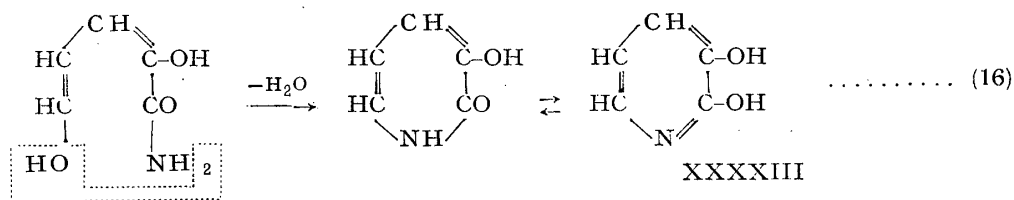
By heating the synthesized XXXXIV in an autoclave, XXXXIII was obtained, but not from pyromucic acid and its ammonium salt. By heating furfural with $HNO(SO_5Na)$[41], which is an intermediate of synthesis of $NH_2OH \cdot HCl$, in place of $NH_2OH \cdot HCl$ in an autoclave, pyromucic acid and its amide (XXXXIV) with XXXXIII were obtained. Those facts indorse the above course (16).

Out of those products in the last experiment, a white needle melting at 135~7° giving a greenish blue color by $FeCl_3$ and having a formula $C_5H_5NO_2$ was obtained. Though the crystal was first thought to probably be XXXXII formed as the first supposed course (15), it was afterwards, by the results of investigation, found to be a mixed crystal of XXXXIII and XXXXIV.

(B) 2,3-Dihydroxy-pyridine and 3-Hydroxy-pyridine from Furfural and Hydrazine-sulfate.[13][10]

By heating furfural with hydrazine-sulfate in an autoclave, 3-hydroxy-pyridine and 2,3-dihydroxy-pyridine were obtained. It was supposed that $NH_2 \cdot NH_2$ would be hydrolyzed into NH_3 and NH_2OH and then the two pyridine derivatives would be produced by reacting those hydrolyzed substances on furfural respectively as shown in the courses (11) and (16).

(C) 2-Methyl-5,6-dihydroxy-pyridine from 5-Methylfurfural and NH_2OHHCl

A white needle of 0.3 g was obtained by heating a mixture of 5-methyl-furfural (XXXXV) 15 g, NH_2OHHCl 10 g and H_2O 150 ml at 155~160° for 3 hours in an autoclave. It melted at 202~3° and gave a deep blue color by $FeCl_3$ and did not form the picrate and its formula was $C_6H_7NO_2$. Its dimethyl ether (XXXXVI) produced by methylation with CH_2N_2 was a colorless liquid, b. p. 89~90°/9 mm and the picrate was a yellow prism, m. p. 121~2°. By oxidation of XXXXVI with $KMnO_4$, a dimethoxy-carboxylic acid (XXXXVII) melting at 175° and forming white needles was obtained, and by demethylation of XXXXVII with HI, a dihydroxy-carboxylic acid (XXXXVIII) was obtained. XXXXVIII was a white prism, m. p. 236~7° and gave a deep blue color by $FeCl_3$ and 2,3-dihydroxy-pyridine (XXXXIII) was obtained by its decarboxylation..

From the above facts, it was presumed that the original crystal would be 2-

methyl-5,6-dihydroxy-pyridine (L) produced as shown in the next similar course as in the case of furfural and NH_2OHHCl.

$$XXXXV \qquad XXXXIX$$

$$\qquad \qquad \qquad \qquad \qquad L \qquad \qquad \cdots \cdots \cdots (17)$$

The fact indorses its presumption that the crystal was obtained by heating the synthesized 5-methyl-furyl-2-caboxylic amide (XXXXIX) with H_2O in an autoclave. Also, the same crystal was obtained by alkali fusion of 2-methyl-5-hydroxy-pyridine as 2,3-dihydroxy-pridine was obtained from 3-hydroxy-pyridine by the Kudernatsch method[57]. From the facts, it is clear that the crystal is L and accordingly, XXXXVI, XXXXVII and XXXXVIII are respectively 2-methyl-5,6-dimethoxy-pyridine, 5,6-dimethoxy-pyridine-2-carboxylic acid and 5,6-dihydroxy-pyridine-2-carboxylic acid.

$$L \qquad XXXXVI \qquad XXXXVII$$

$$XXXXVIII \qquad XXXXIII \qquad \cdots \cdots \cdots \cdots (18)$$

Since the properties of L were similar to that of the substance which Feist[42] synthesized by saponification and decarboxylation on methyl-dihydroxy pyridine-carboxylic acid ester (LIII) obtained by passing NH_3 gas into a ether solution of oxal-acetic ester (LI) and monochloro-acetone (LII), and supposed to be 2- or 3-methyl-5,6- dihydroxy-pyridine, there was no depression on mixed melting of L and the Feist's substance. Therefore, it was presumed that LIII woud be 2-methyl-5,6-dihydroxy-pyridine-4-carboxylic acid ester produced as follows :

$$
\begin{array}{ccc}
\text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 & \text{COOC}_2\text{H}_5 \\
| & | & | \\
\text{CH}_2 & \text{CH}_2 & \text{C H} \\
\end{array}
$$

structure LI $\xrightarrow{\text{NH}_3}$ structure LII $+$ $\begin{array}{c}\text{CH}_2\text{Cl} \\ | \\ \text{CO} \\ \backslash \\ \text{CH}_3\end{array}$ $\xrightarrow[-\text{H}_2\text{O}]{-\text{HCl}}$ structure (ring)

$$
\ce{OC\\ OC} \quad \ce{OC_2H_5}
$$

LI

LII

$$\rightleftarrows \quad \text{HO-C} \quad \text{CH} \qquad \qquad \cdots\cdots\cdots\cdots\cdots\cdots\cdots (19)$$

$$\text{HO-C} \quad \text{C-CH}_3$$

LIII

(D) 2-Methyl-3,6-dihydroxy-pyridine from Furylmethylketone and NH₂OHHCl.[16)

By heating furylmethylketone (XXXX) 5.7 g, NH₂OHHCl 4.4 g and H_2O 50 ml at 155~160° for 2 hours in an autoclave, a colorless needle of 0.1 g was obtained.

It melted at 243~5° and gave a deep reddish violet color by FeCl₃ and its formula was $C_6H_7NO_2$ and its diacetate was a colorless plate melting at 80°. From the difference for the oxime of XXXX, its microanalysis and its FeCl₃ reaction, the crystal may be probably 2-methyl-3,6-dihydroxy-pyridine (LIV) produced as follows :

XXXX $\xrightarrow{\text{NH}_2\text{OH}}$ (furan ring with C-CH₃, NOH) $\xrightarrow{\text{H}_2\text{O}}$ (ring with C-OH, C-CH₃, HO, NOH)

$$\xrightarrow{-\text{H}_2\text{O}} \quad \text{(ring)} \qquad \qquad \cdots\cdots\cdots\cdots\cdots\cdots\cdots (20)$$

LIV
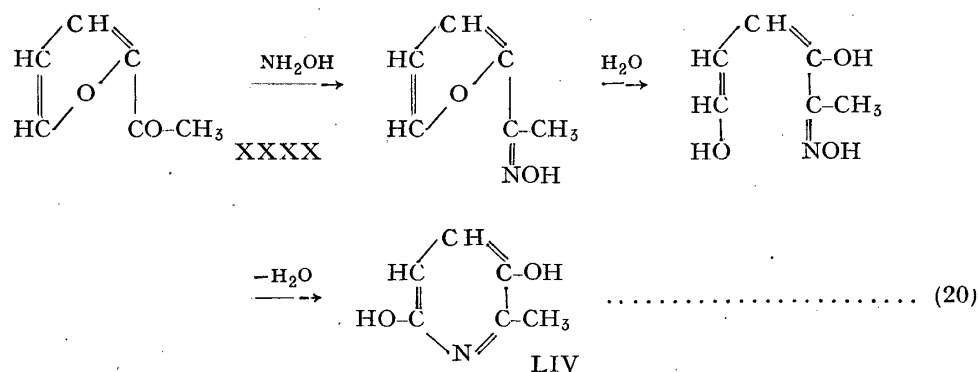
[VIII]   Products Obtained by Heating Pentose with NH₂OHHCl in an Autoclave[10)

3-Hydroxy-pyridine (III) 0.4 g and 2,3-dihydroxy-pyridine (XXXXIII) 0,1 g were obtained by heating xylose 55 g, NH₂OHHCl 25 g and H_2O 400 ml at 155~160° for 3 hours in an autoclave. It was supposed that XXXXIII was

produced by NH_2OHHCl reacting on furfural converted from xylose as the above described course (16), and III was formed by reacting NH_4Cl, which were derived from the reduction of NH_2OHHCl by sugar, on furfural as shown in the course (11). A sufficient amount of NH_4Cl was actualy present in the above decomposed solution.

[IX] Products Obtained by Heating Hexoses with Ammonium Salts or NH_2OHHCl

(A) Products Obtained from Hexose and NH_4-salts

By heating glucose with $(NH_2)_2SO_4$ in an autoclave on the idea that if hexose was used instead of pentose, 2-hydroxymethyl-5-hydroxy-pyridine (LV) may be obtained in place of 3-hydroxy-pyridine as shown in the following course (11), thereby involving 5-hydroxymethyl-furfural (LVI) as an intermediate, three crystals melting at 124~5°, 166~7° and 202~3° showing together the similar absorption spectrums were obtained.

$$\cdots\cdots\cdots\cdots (21)$$

(i) 2-Hydroxymethyl-5-hydroxy-pyridine[9]

The crystal melting at 124~5° was a colorless scaly plate (from ligroin) and had a formula $C_6H_7NO_2$ and was easily soluble in water and ethanol, and gave a reddish brown color by $FeCl_3$ and the picrate was a yellow prism, m.p. 182~3°. Thinking that this crystal may be the above presumed LV, I applied the method[43] by which a large amount of benzoic acid and a little of toluol were produced by alkali fusion at about 200° of benzyl alcohol having a CH_2OH group.

$$\cdots\cdots\cdots\cdots (22)$$

The result was that a large amount of an acidic substance melting at 258~9° and a very little amount of 2-methyl-5-hydroxy-pyridine (XXXIX) were obtained. The acid had a formula $C_6H_5NO_3$ and was a colorless plate (from water) and had one molecule of crystal water and gave a yellowish red color by $FeCl_3$. Those properties were same to that of 3-hydroxy-pyridine-2-carboxylic acid (LVII), and by dry distillation of LVII with lime, 3-hydroxy-pyridine (III) wa obtained. From the above facts, the crystal melting at 124~5° should be the presumed LV.
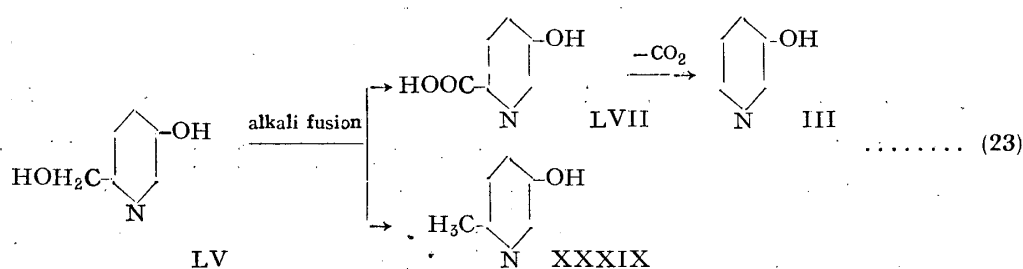
Also, LV and the crystal melting at 202~3° were obtained by similarily heating the synthesized 5-hydroxymethyl furfural (LVI), 5-chloromethyl furfural and 5-ethoxymethyl-furfural with $(NH_4)_2SO_4$ in an autoclave.

(ii)　2-Methyl-5-hydroxy-pyridine[8]

The crystal melting at 166~7° was a colorless prism and gave a red color by $FeCl_3$ and its picrate was a yellow prism, m. p. 203~4°, and it gave no depression of melting point on mixed melting with the above obtained 2-methyl-5-hydroxy pyridine (XXXIX). It was supposed that XXXIX would be produced by reacting 5-methyl-furfural, which would be obtained by the reduction of 5-hydroxymethyl-furfural, with NH_4-salt as shown in the above described course (13).

(iii)　2-Methyl-5,6-dihydroxy-pyridine[10]

The crystal melting at 202~3° was a silky one and had a formula C_6H_7NO and formed no picrate and gave no depression of melting point mixed with 2-methyl-5,6-dihydroxy-pyridine (L).

I previously[10] reported that L would be formed by the intramolecular rearrangement of 5-hydroxymethyl-furfural (LVI), which is an intermediate converted from hexose, to 5-methyl-furan-2-carboxylic acid (LVIII) and producing the amide (XXXXIX) from LVIII and NH_3 and then, reacting as the above described course (17). Subsequently another course (24) was thought in addition to the course (17) that, because of no yields of L by reacting LVIII with NH_4-salt, LVI would be changed to its imide (LIX) and to XXXXIX

by its intramolecular rearrangement and then to L.

$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (24)$$
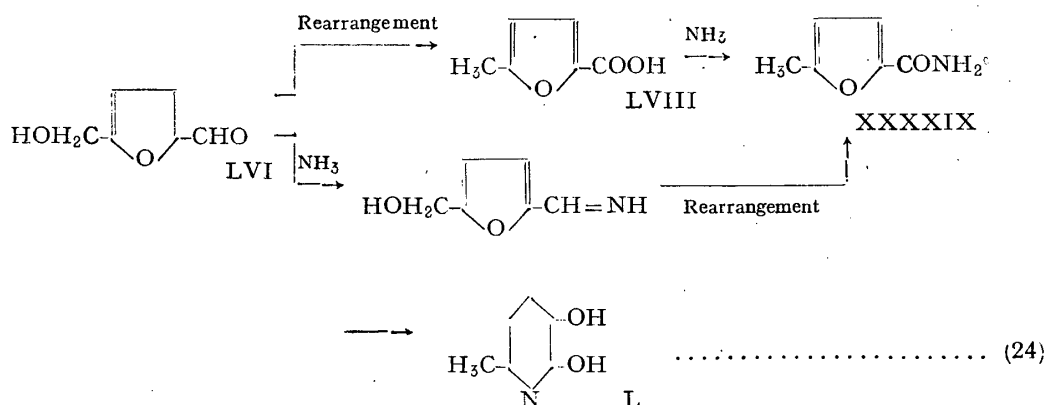
Table 3 shows the formation conditions and yields of the three crystals and yields of levulinic acid obtained together.

Table 3.

Composotion cf decomposition solution			Temp. (°C)	Time (hr)	Yields	
Sugar (g)	NH$_4$-salts (g)	H$_2$O (g)			Base (g)	Levulinic-acid (g)
(A) G. 100	NH$_4$Cl 15	100	155~158	1	0.1	17
G. 200	NH$_4$Cl 70	600	155~160	3	0.2	40
S. 100	NH$_4$Cl 15	300	155	3	0.2	25
S. 100	NH$_4$Cl 15	300	160~165	3	0.4	—
S. 100	(NH$_4$)$_2$SO$_4$ 15	300	155	3	0.4	15
S. 100	(NH$_4$)$_2$SO$_4$ 40	300	155~160	5	1.0	—
(B) G. 500	(NH$_4$)$_2$SO$_4$660	5,000	145~7	3	0.2	—
S. 100	Ammonium-Oxalate 40	500	155~160	3	0.2	—
(C) G. 20	(NH$_4$)$_2$SO$_4$ 20	200	155~160	2	0.1	—
S. 500	(NH$_4$)$_2$SO$_4$200	5,000	152~157	2	0.1	43

(A) : The crystal of m.p. 124~125°
(B) : The crystaJ of m.p. 166~167°
(C) : The crystal of m.p. 202~203°
G. : Glucose. S. : Sucrose. — : Not examined.

(iv) Formation of Levulinic acid from Hexoses and NH$_4$-salts[8]

It is of interest that a comparatively good yields of levulinic acid (LX) with a little of β-hydroxy-pyridines were produced from hexoses and NH$_4$-salts, and it was supposed that LX would be formed as the formation mechanism of Pummerer and Gump[44].

$$\text{Hexose} \xrightarrow{-3H_2O} \underset{\text{LVI}}{\text{HOH}_2\text{C}\!\!-\!\!\overset{\displaystyle\fbox{}}{\underset{O}{}}\!\!-\!\!\text{CHO}} \xrightarrow{2H_2O} \underset{\text{LX}}{\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\ \text{CH}_2\cdot\text{COOH} + \text{H}\cdot\text{COOH}} \qquad (25)$$
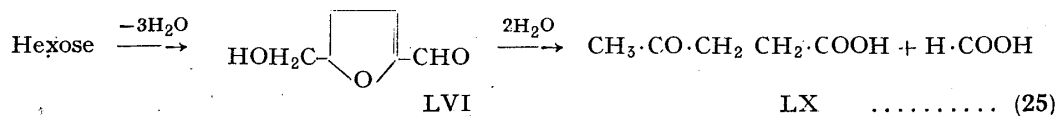
Moreover, high yields of LX are reported by Yabuta (55.3 %)[45], Shimizu and Takei (64 %),[46] and Haworth and Wiggins (72 %).[47]

(B) Products Obtained by Heating Hexose with NH₂OHHCl in an Autoclave[10]

Though hexose with NH_2OHHCl was heated in an autoclave, no pyridine base was isolated as in the case of xylose, but levulinic acid and succinic acid were obtained.

(i) Glucose 75 g+NH_2OHHCl 25 g+H_2O 400 ml $\xrightarrow{\quad 155\sim166°\quad}{3\,\text{hrs}}$ → Levulinic acid
    11 g

(ii) Sucrose 100 g+NH_2OHHCl 40 g+H_2O 300 ml $\xrightarrow{\quad 155\sim160°\quad}{3\,\text{hrs}}$ → Levulinic acid
    8 g+Succinic acid 0.2 g

More experiments are necessary to determine the results.

[X] Folin-Denis and Gibbs color reaction of β-Hydroxy-pyridines[10]

Table 4.

	Folin-Denis-reaction	Gibbs-reaction
3-Hydroxy-pyridine	deep blue	blue
2-Methyl-5-hydroxy-pyridine	"	no color
2, 3-Dihydroxy-pyridine	"	"
2-Hydroxymethyl-5-hydroxy-pyridine	"	"
2-Methyl-5, 6-dihydroxy-pyridine	"	"

From the above table, the five β-hydroxy-pyridines gave a blue color by Folin-Denis phenol reagent as mentioned in the report[48] of Kuhn and Wendt, but Gibbs reaction that hydroxy-pyridines containing no substituted group at the para-place for the hydroxy-group give a blue color by 2,6-dichlorochinon-chloroimide at a slight alkalinity as stated in the report[49] of Stiller and his coworkers, was not suitable for the case of dihydroxy-pyridines.

[XI] Summary of β-Hydroxy-pyridine Homologs

(A) Formation Mechanism of β-Hydroxy-pyridines

(i) The following course (26) showed a general one in which β-hydroxy-pyridines were obtained by heating polyuronides, sugars or furfural with am-

monium salts in an autoclave.

$$
\begin{array}{c}
\text{Polyuronides} \\
\text{Sugars}
\end{array} \longrightarrow
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{R'-C} \diagup \text{O} \diagdown \text{COR}
\end{array}
\xrightarrow{\text{NH}_3}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{R'-C} \diagup \text{O} \diagdown \underset{\parallel}{\text{C-R}} \\
\text{NH}
\end{array}
\xrightarrow{\text{H}_2\text{O}}
$$

$$
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\underset{|}{\text{R'-C}} \quad \underset{\parallel}{\text{C-R}} \\
\text{HO} \quad \text{NH}
\end{array}
\xrightarrow{-\text{H}_2\text{O}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\text{R'-C} \diagdown \quad \diagup \text{C-R} \\
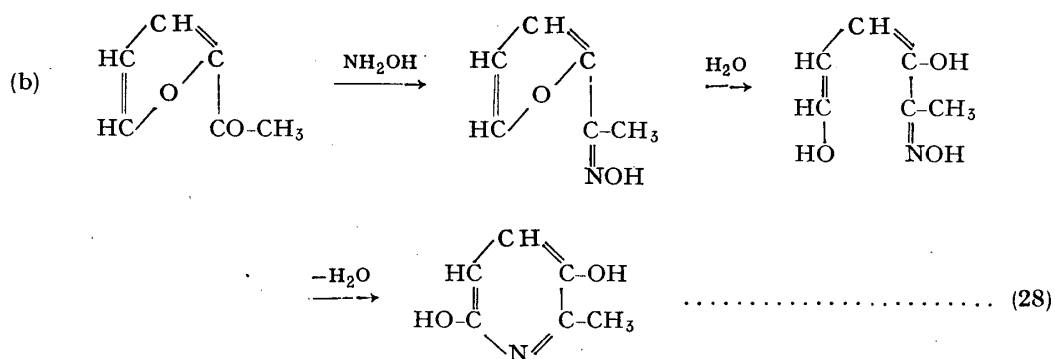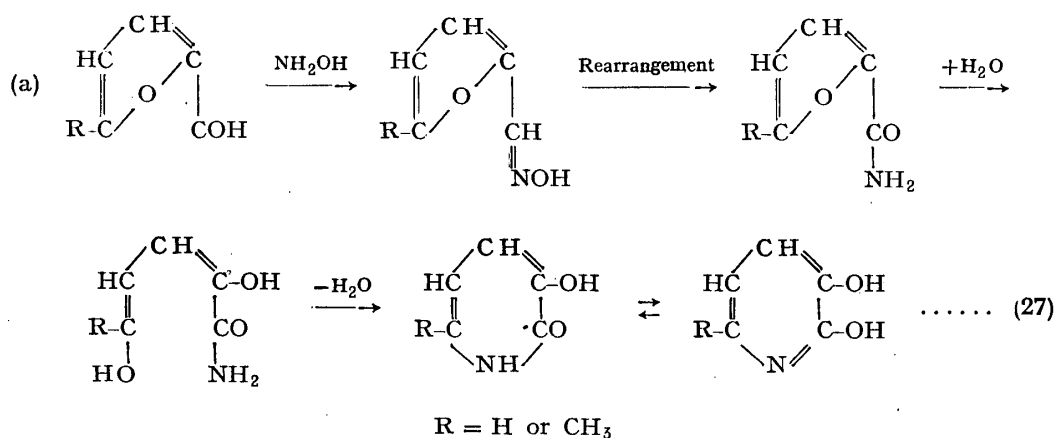\text{N}
\end{array}
\qquad \dots\dots\dots\dots \quad (26)
$$

R = H or CH₃,   R' = H, CH₃ or CH₂OH
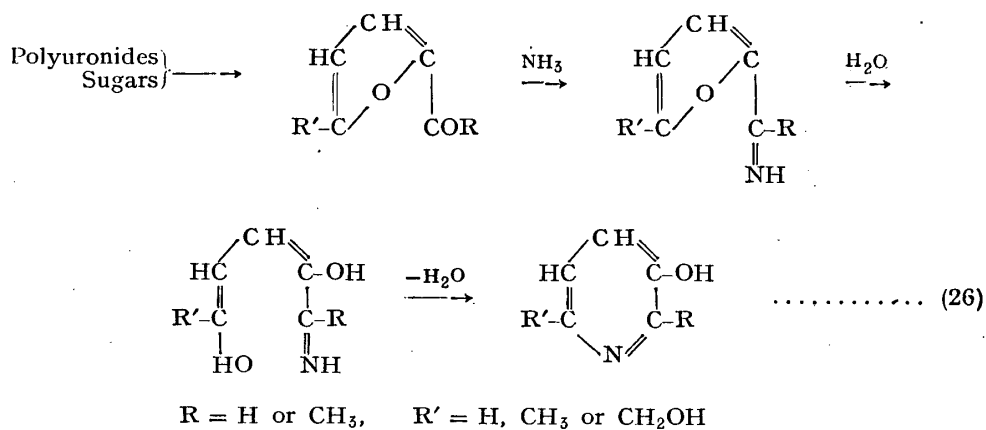
(ii) When NH₂OHHCl was used instead of NH₄-salt, the two following courses (27) and (28) were thought.

(a)
$$
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{R-C} \diagup \text{O} \diagdown \text{COH}
\end{array}
\xrightarrow{\text{NH}_2\text{OH}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{R-C} \diagup \text{O} \diagdown \underset{\parallel}{\text{CH}} \\
\text{NOH}
\end{array}
\xrightarrow{\text{Rearrangement}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{R-C} \diagup \text{O} \diagdown \underset{|}{\text{CO}} \\
\text{NH}_2
\end{array}
\xrightarrow{+\text{H}_2\text{O}}
$$

$$
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\underset{|}{\text{R-C}} \quad \underset{|}{\text{CO}} \\
\text{HO} \quad \text{NH}_2
\end{array}
\xrightarrow{-\text{H}_2\text{O}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\text{R-C} \quad \cdot\text{CO} \\
\text{NH}
\end{array}
\rightleftarrows
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\text{R-C} \quad \underset{|}{\text{C-OH}} \\
\text{N}
\end{array}
\quad \dots\dots \quad (27)
$$

R = H or CH₃

(b)
$$
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{HC} \diagup \text{O} \diagdown \text{CO-CH}_3
\end{array}
\xrightarrow{\text{NH}_2\text{OH}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C}} \\
\text{HC} \diagup \text{O} \diagdown \underset{\parallel}{\text{C-CH}_3} \\
\text{NOH}
\end{array}
\xrightarrow{\text{H}_2\text{O}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\underset{|}{\text{HC}} \quad \underset{\parallel}{\text{C-CH}_3} \\
\text{HO} \quad \text{NOH}
\end{array}
$$

$$
\xrightarrow{-\text{H}_2\text{O}}
\begin{array}{c}
\underset{\parallel}{\text{HC}} \overset{\text{CH}}{\diagdown} \underset{|}{\text{C-OH}} \\
\text{HO-C} \diagdown \quad \diagup \text{C-CH}_3 \\
\text{N}
\end{array}
\qquad \dots\dots\dots\dots\dots\dots \quad (28)
$$

More investigation of those formation mechanisms, and abundant yields of those pyridines are necessary. By progress in the development of those

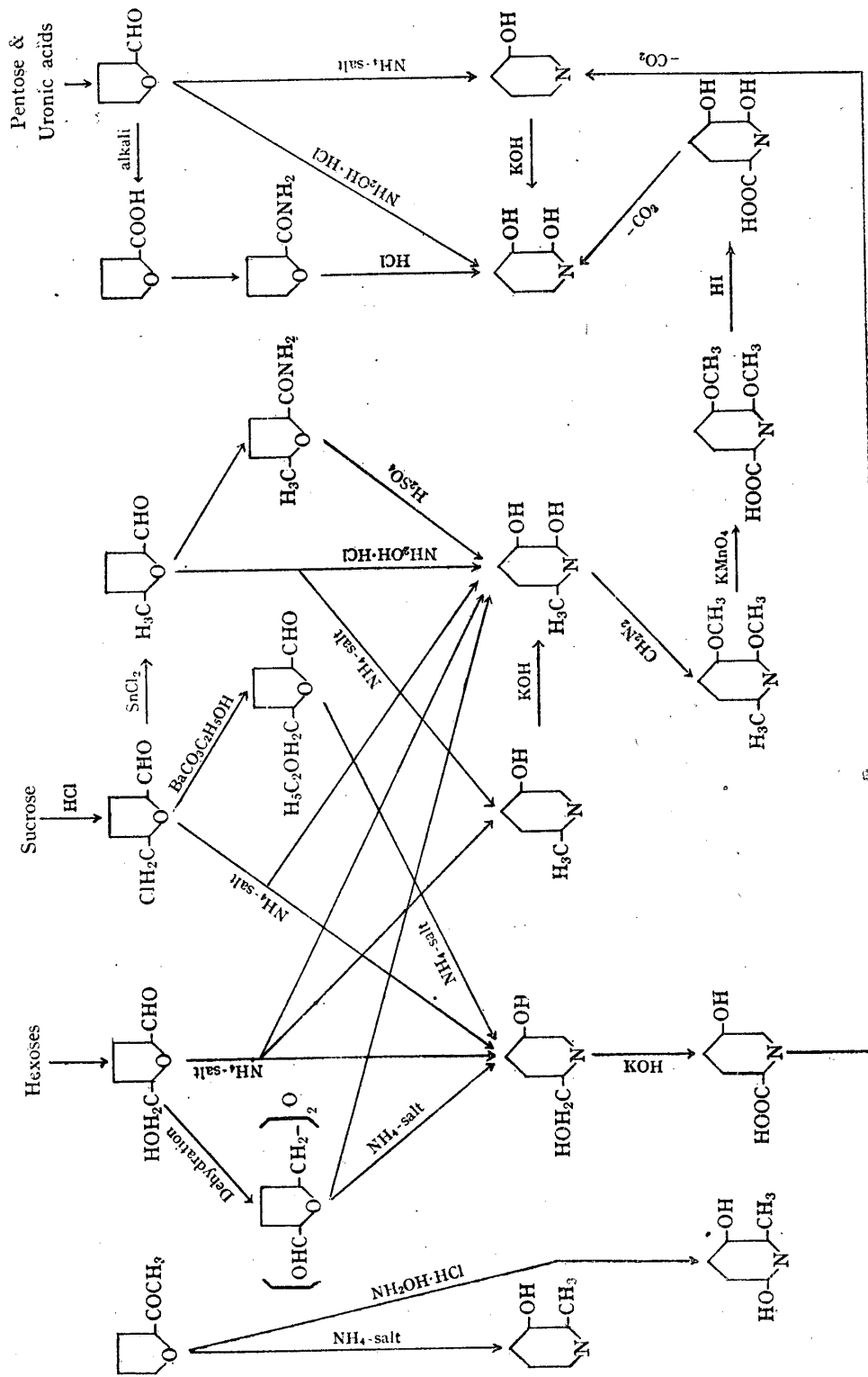**(B) Figure of β-Hydroxy-pyridines obtained**

Fig. 2.

mechanisms, it is hoped that drugs and chemicals containing pyridine nucleus will be produced easily and abundautly from cheap furfurals and sugars. Also, it is supposed that the above described mechanisms followed with deoxygenation by carbon may be one of the mechanisms of formation of pyridines from dry distillation of coal.

Moreover, it is very interesting that several patents[50][51][52] on the production of pyridine from hydrofuryl-carbinol and ammonia were recently announced.

[XII] Total Summary

Alginetin (2-methyl-3,8-dihydroxy-chromone) by heating alginic acid with water in an autoclave, reductic acid by heating polyuronides in acidic solution in an autoclave, and 3-hydroxy-pyridine by heating brown algae in an autoclave were obtained.

I presumed those formation mechanisms and obtained several β-hydroxy pyridine derivatives from furfurals or sugars and NH_4 salts or $NH_2OH \cdot HCl$ by developing the formation machanism of 3-hydroxy-pyridine.

Acknowledgment

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