β-Acid as One of the Nutritive Factors.
(Synthesis of β-acid.)

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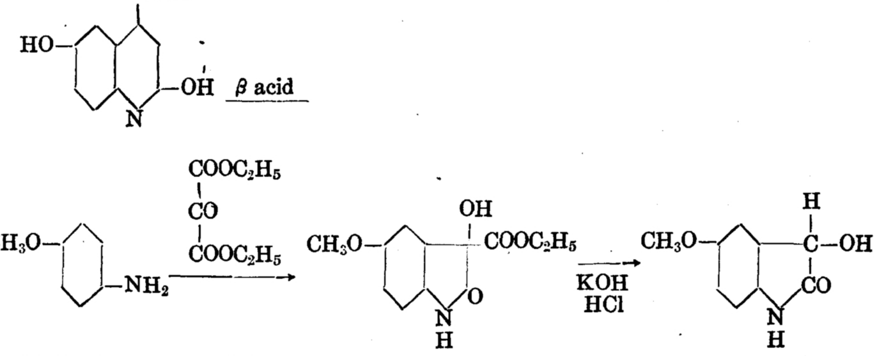
On the way of research for *p-p*-factor, as nicotinic acid has not always satisfied the aim of curing pig-pellagra, we came to the opinion that there might be at least another factor that resembles in its chemical charactor to nicotinic acid but plays a little different physiological rôle. It seems reasonable to call nicotinic acid antiglossitic factor, because it cures very well a sort of epidemic glossitis which happens very often at the climate change among students living in the boarding-houses and must be thought of avitaminous nature. (This glossitis may be perhaps analogous to Canine black tongue.) Recently we became to suppose that the fraction which yields β-acid* on HCl-hydrolysis might be necessary for higher mammals as one of vitamin B-complex. According to our animal expermients it was seen that β-acid could not only sustain the acute fall of the body weight, but also, accompanied with the purified ricebran-extract, make the increase of body weight of dogs, which were fed with the following deficient diet.

Purified cornstarch	80	NaCl	1
Purified casein	10	Olive oil	5
Calc. phosph.	1	Cod liver oil	2
Calc. carb.	1		

The experiment which is now in progress by using the yellow corn in place of purified cornstarch will yield more satisfactory results, as the dogs hate to take diet consisting of purified cornstarch.

β-acid has been isolated by B. Suzuki from acid-hydrolysates of crude

Fig. 1



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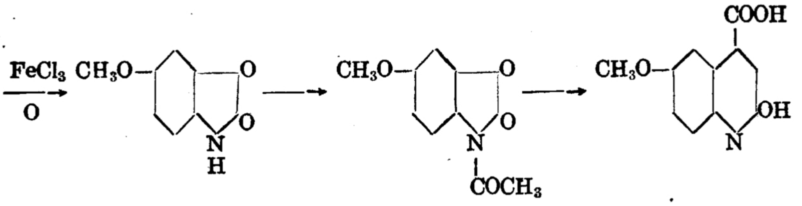
* B. Suzuki and K. Sahashi.



oryzanin and its constitution has been established by K. Sahashi(1). The methylether of β-acid has been synthesised by Halberkann(2) in the following routs.

We also tried to make this substance. Our first effort was to desaminise the 2-hydro-oxy-6-amino-quinoline-carboxylic acid (4), which was synthesised in the following way, but no use, for the aminoquinolin-compound was very resistant towards $NaNO_2+HCl$ or $NaNO_2+H_2SO_4$. The hot mixture of aminoquinoline, sodium nitrite and sulphuric acid was poured into a hot solution of 10% $CuSO_4$, but no marked evolution of nitrogen took place. Next we tried to convert 2-oxy-6-bromoquinoline-carboxylic acid (4) to dihydro-oxy-compound in the following manner.

Fig. 2

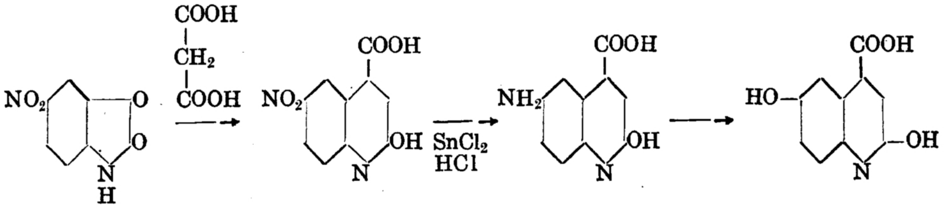
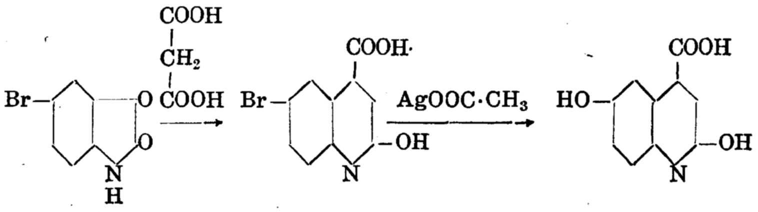


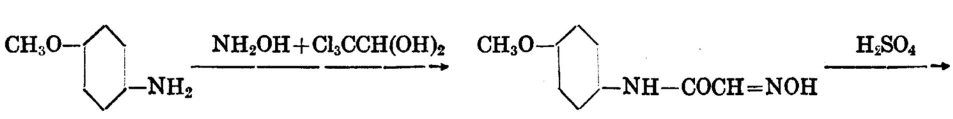
Fig. 3



But the separation of dihydro-oxyquinoline-carboxylic acid from silver bromide was not succeeded.

Finally we obtained the desired substance in the following manner.

Fig. 4.



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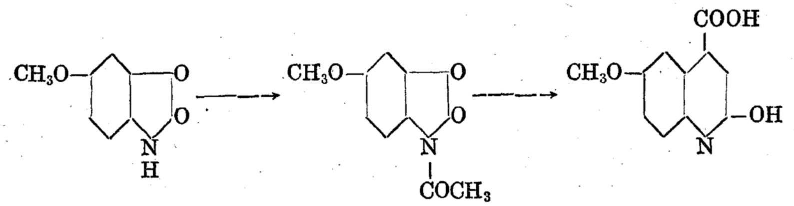
(1) K. Sahashi, *Biochem. Z.*, **189** (1927), 208.
(2) J. Halberkann, *Ber. deut. chem. ges.*, **54** (1921), 3079.



While the yield of the isonitroso compound was satisfactory, the way from this to the methoxy-isatin was not so smooth. In spite of changing the condition by that the oxime was converted to the methoxy-isatin by concentrated sulphuric acid the improvement of the yield was not achieved.

β-Acid was obtained in the usual manner by heating the methylether with HI⁽¹⁾.

β-Acid seems to promote the growth of silk-grass, when it sprouts. It can not be excruded that the β-acid will act as some phytohormone.

Experimental.

6-Nitro-2-hydroxy-quinoline-carboxylic acid (4).

5-Nitroisatin was condensed with malonic acid in glacial acetic acid in the usual manner. F. 208°.

$C_{10}H_6O_5N_2+1^1/_2H_2O$(261)	Calc.	C	45.97%	Found	C	45.39%
		H	3.47%		H	3.57%
		N	10.73%		N	10.56%

Ethylester of 6-nitro-2-hydroxy-quinoline-carboxylic acid (4). F. 195°.

$C_{12}H_{10}O_5N_2+H_2O$(280)	Calc.	C	51.43%	Found	C	51.05%
		H	4.29%		H	4.35%
		N	10.00%		N	10.03%

6-Amino-2-hydroxy-quinoline-carboxylic acid (4).

3.2 g. of 6-nitro-2-hydroxy-quinolin-carboxylic acid (4) was dissolved in alcohol and reduced with 19 g. of stannous chloride in 800 concentrated hydrochloric acid at 100°. The tin-double-salt was filtered, suspended in water and decomposed with hydrogen sulphide. After filtration the filtrate was concentrated to a small volume, which separated a crystalline deposit. F. over 300°.

$C_{10}H_8O_3N_2 \cdot HCl+H_2O$.	Calc.	C	46.5%	Found	C	46.5%
		H	4.2%		H	5.5%

6-Bromo-2-hydroxy-quinoline-carboxylic acid (4).

This compound was obtained by the condensation of 5-bromo-isatin with malonic acid in glacial acetic acid. F. 218–220°.

$C_{12}H_{10}BrO_3N$(296)	Calc.	C	48.64%	Found	C	48.58%
		H	3.37%		H	3.52%
		N	4.71%		N	4.44%

2,5-Dihydroxy-quinoline-carboxylic acid (4) (+silver bromide).

The bromo-quinoline compound was converted with silver acetate by heating in water on the water bath and then in the oil bath.

$C_{10}H_7O_4N+AgBr$(377)	Calc.	N 3.71%	Found	N 3.55%

p-Methoxy-isonitroacetanilide.

This compound was obtained from *p*-anisidine, hydroxylamine and chlorhydrate. The synthetic process is almost the same as described by Marvel and Hiers⁽³⁾ in the preparing of isonitroacetanilide. The yield is more than 70% of the theoretical amount. The product was recrystallized from hot water. F. 178°–179°.

$C_9H_{10}O_3N_2$(194)	Calc.	C 55.67%	Found	C 56.04%
		H 5.15%		H 5.02%
		N 14.43%		N 14.23%

5-Methoxy-isatin.

This compound was prepared by the action of concentrated sulphuric acid on *p*-methoxy-isonitrosoacetanilide, as described by Marvel in preparing isatin. Many runs were made in which the concentration and the amounts of sulphuric acid and the reacting temperature are varied over a considerable range, nevertheless the yield of methoxy-isatin could not be improved (not more than 10% of the theoretical amount). The compound was recrystallized from glacial acetic acid. F. 195°.

$C_9H_5O_3N$.	Calc.	C 60.03%	Found	C 60.19%
		H 3.95%		H 3.86%
		N 7.93%		N 8.38%

1-Acetyl-5-methoxy-isatin.

This compound was obtained by the acetylation of methoxy-isatin with acetic anhydride. F. 145°.

2-Hydroxy-quinoline-carboxylic acid.

This acid was prepared by heating of acetylmethoxy-isatin with sodium hydroxide and then acidifying with sulphuric acid. F. 326°.

2,6-Dihydroxy-quinoline-carboxylic acid (4) (β-acid).

This compound was obtained by heating of methoxy-β-acid with 10% HI. This purifications procedure was the same as described by Sahashi. F. 337° (with decomposition).

$C_{10}H_7O_4N+H_2O$(223)	Calc.	C 53.81%	Found	C 53.73%
		H 4.03%		H 4.07%
		N 6.27%		N 6.08%

The authors are indebted to Nippon-Gakujutsushinkokai as well as to South Manchuria Railway Company for grants in aid of this research. They also wish to express their thanks to the analytical department of Takeda Shoten for the microelementary analysis.

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(3) C. S. Marvel and G. S. Hiers, "Organic Synthesis", collect. vol. I, 321.