

Biochemical Studies on Pityrol, I.

Introduction to the Biochemistry of Pityrol

By

Shigeru Komatsu

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It was said, in Japan, that a brownish-black tarry substance which was formed from rice bran by burning a small quantity slowly on a piece of Japanese paper stretched across the mouth of a teacup, and the tar which allowed to drop into the cup through the scorched paper, has been used as an infallible remedy for certain skin diseases such as eczema.

Dr. Matsuura, a former Professor of the Department of Medicine of our University, investigated in a clinical experiment the rice bran tar named "Pityrol" by him, which was obtained, according to tradition, by dry distillation of rice bran in a retort, and the value of this product as an important remedy for skin diseases began to be admitted by every body, and much attention has been paid to a study of the effect of the crude drug upon patients. However, nothing was yet known concerning the active principle of the crude drug, the relation between the chemical constituents of the tar and their pathological action, and also the chemical changes which take place in the constituents of the rice bran during the process of distillation, and these problems of the rice bran tar awake the interest of the present writer, and started him on this study, in connection with the pathological investigation by Professor Matsumoto of the Dermatological Institute of the Department of Medicine, the successor of Professor Matsuura. The writers' biochemical investigations into pityrol are, therefore, of value only when taken together with the pathological study by Professor Matsumoto.

The rice bran which was prepared by means of a milling machine designed by Mr. Tsuge, from the rice named "Shinriki", grown near Osaka, was subjected to dry distillation in Fischer's aluminum retort. It was noticed that a colourless oil begins to distil with some water at about 200°, the colour of the distillate becoming darker as the amount increases, and the temperature rises. The main reaction which takes place between 350° and 400° with the formation of a dark brown-coloured tar and large quantities of a combustible gas, and at 450° the reaction is completed. The yield of tar, coke, aqueous liquor and gas was 24%, 28%, 36% and 12% respectively.

The tar, thus obtained, was a dark brown viscous liquid containing some carbon particles and having a peculiar odour, and soluble in alcohol, acetone and benzene. In order to learn in the chemical nature of the tar, it was divided into two parts-volatile and non-volatile, and each part was further divided into acidic, basic and neutral parts with the results (A) shown in Table I.

To attain our purpose, the pityrol obtained through the courtesy of Mr. S. Ichinose, Director of the Shinyaku Kaisha, Kyoto, was meticulously investigated as to its chemical constituents.

Table I.

		A	B	C
Tar		24 %	15 %	—
Coke		28 "	31 "	—
Aqueous liquor		36 "	40 "	—
Gas		12 "	14 "	—
Tar	{ Volatile part	13 "	17 "	12 %
	{ Non-volatile part	87 "	83 "	88 "
Tar	{ Neutral part	67 "	50 "	57 "
	{ Acidic "	29 "	37 "	37 "
	{ Basic "	4 "	13 "	6 "
Volatile part	Neutral	66 "	44 "	89 "
	Acidic	30 "	39 "	6 "
	Basic	4 "	16 "	5 "
Non-volatile part	Neutral	68 "	55 "	52 "
	Acidic	29 "	55 "	41 "
	Basic	3 "	10 "	7 "

The percentage of the various fractions (C) in commercial pityrol, as investigated by Mr. Sakami, seems to differ slightly from that obtained on a laboratory scale (A) by Dr. Fujita.

According to the pathological study of the tar and its constituents which was carried out in the laboratory of Professor Matsumoto,¹ these substance being applied repeatedly to the skin of a rabbit's ear, the degree of inflammation and the evidence of irritation differed according to the differing constituents of each substance; the larvae of mosquitoes, and maggots were affected by the acidic fraction most strongly, while the neutral fraction proved to be most mild. Differing symptoms of intoxication due to the differing nature of fraction were also noticed when these fractions were administered to mouse or snake subcutaneously or by inhalation. The most interesting symptom of the non-volatile neutral fraction which boiled at above 250° under 10 mm., was that when applied repeatedly to the inner surface of a rabbit's ears, malignant epithelioma was produced, which then terminated in true cancer. However, such a terrible disease on animal skin has never before been observed by applying the pityrol itself.

Hence, certain questions naturally arose in the writer's mind whether other tars produce similar pathological effects on animals and whether the constituents of tar from any substance would be affected by the external conditions under which the materials are subjected to distillation.

Now, it was a well-known fact that a terrible disease has arisen out of the development of the tar industry, and it was said that the tars from coal or vegetable materials have been noticed by many investigators to be a cancer producing factor for the workers in the factories where tars were manufactured or treated to derive useful materials from them. The tar cancer study has been the subject of study by investigators, since the experimental research by Yamagiwa and Ishikawa in producing malignant epithelioma by application of coal tar on a rabbit's ear.²

E. L. Kennaway's investigations³ indicate that the fractions of the coal tars, except blast furnace tar, which boils above 270°, has the cancer producing principle, and accordingly it seems true that the active principle which produces epithelioma on an animal skin will occur in certain tars produced by distilling coals and other vegetable materials under certain conditions, though our knowledge concerning the cancer-producing factor in tars is exceedingly scant.

¹ *Acta Dermato.* **5**, 228; **9**, 383; **10**, 325, 393, 485; **11**, 45, 86.

² *Mit. d. Med. Ges., J. Tokyo*, **30**, 1.

³ *British Med. J.* 564 (1924).

The neutral substances which compose the major part of pityrol perform certain pathological actions on the skin of the rabbit ear, and the chemical constituents of those substances were investigated by Sakami in the following manner.

The volatile neutral part of pityrol was treated with conc. sulphuric acid and fuming sulphuric acid successively on the one hand, and on the other, with liquid sulphur dioxide¹ to separate it into saturated and unsaturated fractions, and it was confirmed as composed of about 80% of unsaturated hydrocarbons; and the percentage of the hydrocarbons of paraffin, an unsaturated and aromatic series, was estimated by the treatment above-mentioned.

In order to isolate the hydrocarbons of the paraffin series only, the oily residue which had been unaffected by the treatment with the sulphuric acids above mentioned, was passed on reduced nickel heated at 300° to remove the polymethylene hydrocarbons, and the reaction product was subjected to fractional distillation after being treated with con. sulphuric acid to remove any aromatic hydrocarbons which would be formed from hexamethylenes by the catalytic oxidation. By repeated fractional distillation, the hydrocarbons C_3H_{18} , C_9H_{20} , $C_{10}H_{22}$, $C_{11}H_{24}$, $C_{12}H_{26}$, $C_{13}H_{28}$, $C_{14}H_{30}$ and $C_{15}H_{32}$ were isolated in a state of purity, among which the hydrocarbons of the carbon atoms C_{10} , C_{11} , C_{12} , & C_{13} were noticed to compose the major part of the neutral volatile oil. The unsaturated hydrocarbons which were supposed to be transformed by the sulphuric acid treatment partly into alcohols,² and partly polymerised into hydrocarbons of high molecular weight,—both of these reaction products were investigated separately—& alcohols of the carbon atoms C_{10} , C_{11} , C_{13} , C_{14} & C_{15} and the hydrocarbons $C_{16}H_{26}$, $C_{18}H_{30}$, $C_{21}H_{35}$, $C_{24}H_{38}$, $C_{28}H_{46}$ were actually confirmed as occurring in the reaction products by isolating them in a fairly pure state by fractional distillation.

When our assumption was admitted to be correct that alcohols will form by treating olefine hydrocarbons with sulphuric acid as a result of the hydrolysis of the alkyl sulphuric acid esters formed by the direct interaction of two substances, and polymerization was the principle result of high unsaturated hydrocarbons by the treatment, though the tendency to form alcohols from olefines decreases with increasing molecular weight, while with increasing molecular weight polymerization becomes the principal result,² and consequently it was concluded that the unsaturated

¹ Edeleanu; *Z. angew. Chem.*, **32**, 175 (1919).

² Michael & Brunel. *Am. Chem. J.*, **41**, 118 (1909).

hydrocarbons which make up the volatile part of the pityrol should be homologues of the series, C_nH_{2n} , & C_nH_{2n-2} , having the carbon atoms C_8 , C_9 , C_{10} , C_{12} & C_{14} .

As to the nature of the neutral compounds in the non-volatile part of the tar, the fractions which separated from each other by distillation, were assumed from the determination of the physical constants and analysis, to be composed of hydrocarbons of the polymethylene series of high molecular weight such as $C_{20}H_{40}$, with some hydrocarbons of the aromatic series.

	Fraction	Yield	d_4^{25}	n_D^{25}	C%	H%
1	to 130° (10 mm.)	10 %	0.8804	1.4837	85.6	11.5
2	130°-180° "	23 "	0.8616	1.4750	85.6	12.4
3	180°-230° "	24 "	0.8999	1.4870	82.3	12.0
4	230°-300° "	13 "	0.9445	1.5270	84.3	11.4

Pityrol, so far as studied, is similar in the nature of its constituents especially of the hydrocarbons to Russian or Japanese Petroleum and the low-temperature coal tar, but not coal tars resulting from high temperature carbonization¹.

The basic part of pityrol though the amount of it was very scanty compared to the other constituents, has an important relation with its physiological actions; the offensive odour of the tar and the decline of appetite of the workers in the laboratory where the tar is treated was frequently noticed, and these facts are due to the presence of the basic compounds.

Suzuki's experiment on the isolation of the basic compounds, indicates that they are composed of tertiary amines with some primary and secondary amines. By repeated fractional distillation, the basic part was divided into fractions, and each fraction was then converted into the double salts of mercuric chloride or picrates. By fractional crystallisation in their aqueous or alcoholic solution, 2-methyl pyridine, 3-methyl pyridine, 2-4-dimethyl pyridine, 2-6-dimethyl pyridine, 2-4-6-trimethyl pyridine, aniline and quinoline were isolated in a pure free state. The fact that the methyl derivatives of pyridine, aniline and quinoline occur in pityrol and probably also in coal tars, aroused the present writer's interest since

¹ C. Engler u. H. v. Höfer: *Das Erdöl* II. (1909). S. Komatsu & S. Kusumoto: *These Memoirs*, 7, 77 (1924); A. R. Warnes: *Coal tar distillation* 1923.

the occurrence of these compounds in tars would have some intimate relation with the chemical transformation which takes place during distillation in the retort, of the organic compounds which are to be found in the raw materials.¹

The acidic part of pityrol, has a connection with some pharmacological action of the tar, was investigated by Masumoto to learn its chemical nature.

The volatile acidic part of pityrol, according to the report made by T. Shimoda², has a highly irritative effect on the rabbit ear, the cutaneous connective tissue being affected most intensely by this compared with other constituents of the tar.

The volatile acidic fraction of the tar, which was isolated by means of a 5% caustic soda solution, was fractionated after being converted into methyl derivatives by means of dimethyl sulphate and caustic soda to avoid their oxidation. Although the pure compound could not be isolated by Masumoto's efforts, the existence of a compound of the molecular formula $C_{10}H_{18}O=C_9H_{15}OCH_3$ in the region of a B.p. 70° - 75° under 7 mm. was assumed by referring to the physical constants and also by the analysis of the fractions resulting by repeated fractional distillation of the methylated oil, but such a compound has never been observed to occur in coal tars.

An interesting comparative study of coal-tars and pityrol by cutaneous injection into rabbit's ears was carried out by Dr. Shimoda² in Professor Matsumoto's laboratory. The experiments indicate that the hyperkeratotic change of the epithelial new-growth due to coal tar is evident, proliferation into the deeper layer being also marked, while both these changes are only slight in the case of pityrol application, and also the proliferative change of the subcutaneous tissue or of the cartilaginous plate of the ear due to the injection of coal-tar is far more evident than that due to pityrol in both cases. Such difference in the pathological action between coal tar and pityrol should be attributed to the difference in quality and quantity of the chemical constituents of the tars, and the hypothesis for the explanation will be granted when the analytical results by Sakami, Suzuki, and Matsumoto on pityrol are compared with those of the coal tars mentioned in the literature.³

The difference in the chemical constituents of both coal and rice

1 A. E. Tschitschibabn: J. p. Chem. **107**, 109, 122 (1924).

2 Acta Dermat. **10**, 500, 578 (1927).

3 A. R. Warnes: Coal tar distillation, 1923.

bran tars will account for the differentiation of the constituents of the raw material and also the external conditions under which the material was subjected to distillation.

Although the development of the chemistry of synthetic colours and drugs brought on a great advance in the coal-tar chemistry, the actual details of the chemical transformations occurring in the distillation of the coal material in the retort are still only known in part; the view proposed by Berthelot¹ that many of the aromatic hydrocarbons in coal tar resulted from high temperature carbonisation, which originated from acetylene by a process of condensation and polymerisation, is now opposed by the "bound" molecular theory² proposed by Jones & Wheeler, in which the hydrocarbons of coal tar can be produced by breaking down the "bound" condition present already in coal of a "bound" molecule which is attached chemically or physically to the non-alkyl groups.

The birth and development of the low temperature carbonization of coals, which has been going on during the decade of this century facilitate the recognition by chemists of the idea that the chemical composition and physical properties of tars are influenced to a wide extent by external conditions such as pressure and temperature under which the destructive distillation of the materials are performed.

Dealing first with physical constants, the lower specific gravity tars of coals are generally produced when low carbonisation temperatures are used, or coals are carbonized in vertical retorts, while the high temperature carbonisation in horizontal retorts usually produces tars of high specific gravity³. The vacuum tar, according to the investigation by Pictet and Bouvier⁴, is composed of a mixture of saturated and of unsaturated hydrocarbons, but with an entire absence of aromatic hydrocarbons, which usually occur abundantly in high-temperature tar. It was, therefore, supposed that most of the compounds found in the high-temperature tars were produced by the thermal decomposition of the compounds previously formed from coals, which were similar or of the same character as the low-temperature tar or the vacuum tar compounds.

It will be of interest to study from this stand point the nature of the distillates obtained from various kinds of coal when they are submitted to destructive distillation under the same conditions; according to the experiment by F. Fischer and W. Glund⁵, the low-temperature tar from lignite

1 M. Berthelot: *Les carbures d'hydrogène I*, 92 (1901).

2 J. Chem. Soc., **105**, 140 (1914).

3 P. E. Spielmann: *The Const. of coal tar*, 2 (1924).

4 C. R., **157**, 1436 (1913); **160**, 629 (1914).

5 Z. angew. Chem., **32**, 337 (1919).

is semi-solid, and from bituminous coal is liquid, and the essential difference between these low-temperature tars, the former tar being composed chiefly of paraffin hydrocarbons, should account for the difference of the chemical constituents of the raw materials from which the tars were obtained.

The experimental results¹, cited here, indicate that the raw material, and the temperature and the pressure of the carbonisation in the retort will greatly affect the quantity & quality of the reaction products—gas, tar and coke.

Material.	Condition.			
	Reduced pressure		Ordinary pressure	
			400°	1000°
Cellulose	tar	45 %	23 %	4 %
	aqueous liquor	32 „	33 „	36 „
	gas	13 „	25 „	10 „
	coke	10 „	17 „	40 „
Lignine	tar	15 „	13 „	—
	aqueous liquor	21 „	12 „	—
	gas	—	18 „	—
	coke	52 „	57 „	—

Various points of interest emerge from these researches; cellulose or allied substances which occur in natural substances in a free state or as a compound, furnishes an acidic substances in the tar, while basic compounds are derived from proteins and other nitrogenous matter. Lignine and resinous substances by destructive distillation will result in the forming of aromatic compounds. However, the relation of the composition of coal to the products of the distillate is rendered difficult by the lack of a true knowledge of the composition of coal, though there is now no need of any discussion as to the vegetable theory of the origin of coal. The problem should be solved in the near future and a solution of the problem, which will be awaited with interest, in dealing with natural substances of known constitution on the one hand, and on the other, by the endeavour to ascertain the chemical nature of coal substances.

The fact that the rice bran yields much more tar in comparison with the quantum derived from peat and wood—a fact obtained from statistics compiled from the results of the experiments of many chemists,—should

¹ Strache—Lant: Kohlenchemie (1924)

be ascribed to the occurrence of protein and fatty substances in a greater amount in the bran than in the other natural substances in which carbohydrates and lignine predominate.

	H ₂ O	Ash	Protein	Fat	Carbohydrates		Lignine
					Simple & disaccharides	Poly-saccharides	
Rice bran	15	9	13	23	12	20	—
Fat-free rice bran	14	12	17	0.7	15	26	—
Woods	—	—	1	1-3	10-25	43-56	20-29
Peats	—	—	—	6-13	10-16	9-18	8-12

	Coke	Aqueous distillate	Tar	Gas
Peat ¹	31-40	36-30	6-10	19-28
Wood ²	38	33	9	20
Rice bran	28	36	24	12

From the analytical figures shown in the table, it was anticipated that the rice bran which had its fatty substance removed by extraction with petroleum ether would yield coke in greater quantum and tar in less degree than the ordinary bran, and the assumption was realized by Fujita's experiment shown in the table. These facts correspond with the hypothesis that tarry matter would have its origin mostly in the open chain carbon compounds, such as fatty and protein substances, and that coke, on the contrary, would be derived from lignine or other closed chain carbon compounds.

The organic matters in the whole rice bran by distillation in the retort were distributed in a ratio of 12.8 : 29.6 : 38.4 : 18.2 to aqueous liquor, coke, tar and gas respectively, while the distribution ratio of the organic matters in extracted bran was altered to 10 : 5 : 8.

The percentage of volatile and non-volatile parts and also that of

1 P. Hoering: Moornutzung u. Torfverwertung (1915), 265.

2 L. F. Hawley & L. E. Wise: The Chemistry of Wood (1926) 195, 201, 304.

the acidic, basic and neutral fractions in both parts were different in two cases (A & B), and we noticed especially a marked difference in the content and properties of the neutral oil, which, according to our theory, would owe its origin principally to the fatty substances in the raw material.

The difference which was noticed in the chemical constitution between the pityrols prepared on technical and laboratory scales, should be attributed to that in the material of the retort and the external conditions, such as temperature, under which the tar was produced.

In order to settle the assumption that the saturated and unsaturated aliphatic hydrocarbons which occur in pityrol were derived from fatty substances in the bran, palmitic and oleic acids which are the chief constituents (20% and 80% respectively) of the fatty acids of the oil, were isolated from the "Haze tallow" and the "Tsubaki oil" in a pure state respectively, and subjected to distillation of their sodium salts in Fischer's aluminium retort.

Professor Pictet¹ has reported sodium stearate gives rise by distillation under reduced pressure to a mixture of liquid or solid hydrocarbons of the series C_nH_{2n+2} ; while Kawai's experimental results as will be seen from the table, differ from the former².

According to the experiment by Shoyama, sodium palmitate by distillation in a retort under ordinary pressure, yielded tar, coke and gas in the following proportions:—

	Tar	Coke	Gas & loss
Stearate (Pictet)	70	20	10
(Kawai)	72	15	13
Palmitate (Shoyama)	70	24	6
Oleate (Pictet)	70	24	6
(Kawai)	63	28	9
(Ogata)	65	17	18

Sodium oleate, under the same conditions as palmitate, was noticed by Ogata to decompose into tar, coke and gas with the yield shown in the table.

¹ Hel. Chim. Acta, **2**, 501 (1919)

² J. Soc. Chem. Ind., (Japan) **27**, 56 (1924)

Although there is no marked difference among the experimental results of the organic acids by different investigators into the yield of tar, coke and gas, as shown in the table, the relative proportions of volatile and non-volatile parts, and of saturated and unsaturated compounds in the tars will be noticed to differ from each other owing to the difference in the conditions under which the acids were distilled.

	V. p.	N-v. p.	Saturat.	Unsaturat.
Stearate (Pictet)	—	—	100	—
(Kawai)	—	—	40	60
Palmitate (Shoyama)	45	55	38	62
Oleate (Pictet)	—	—	—	100
(Kawai)	—	—	37	63
(Ogata)	47	53	20	80

S. Kawai has reported that by distillation under ordinary pressure of the calcium salts of stearic and oleic acids, saturated and unsaturated hydrocarbons were obtained in both cases, though the pure hydrocarbons could not be isolated from the tars, while Pictet and his coworkers had described the hydrocarbons of the series C_nH_{2n+2} from stearic acid and those of the series C_nH_{2n} from oleic acid as being only reaction products.

Shoyama has endeavoured to isolate pure hydrocarbons from the distillation product and has succeeded in the isolation of the saturated and unsaturated hydrocarbons of the carbon atoms from C_6 to C_{14} , in a fairly pure state from the volatile part of the tar, and those of C_{13} – C_{30} from the non-volatile part. The main constituents of the neutral part of the tar were the hydrocarbons of the C_nH_{2n} series, C_3H_{16} , $C_{10}H_{20}$, $C_{11}H_{22}$, $C_{13}H_{26}$, $C_{15}H_{30}$, $C_{20}H_{40}$, $C_{30}H_{60}$, and also those of the C_nH_{2n+2} series C_3H_{18} , C_9H_{20} , $C_{12}H_{26}$, $C_{14}H_{30}$, $C_{15}H_{38}$, $C_{20}H_{42}$, and the results agree fairly well in their statement of the constant of the hydrocarbons with those announced by Sakami from the neutral part of pityrol.

Under the same conditions as the palmitic acid, sodium oleate was noticed to yield of the hydrocarbons of the carbon atom C_7 , C_8 , C_9 , C_{10} , C_{11} , C_{15} , C_{16} , C_{17} , of the C_nH_{2n} series as a principal constituent of the distillate with some saturated hydrocarbons C_9H_{20} , C_3H_{18} & C_7H_{16} , and these unsaturated hydrocarbons were previously isolated by Pictet from

the distillation product of sodium oleate under reduced pressure, and were also confirmed by Sakami to occur in the neutral volatile part of pityrol.

As to the fate of pentosan, cellulose and other soluble carbohydrates in the rice bran during the distillation in the retort, we have at present no exact knowledge as to the products therefrom. However, as it was stated by Klason, Heuser & Scherer¹ that the pentosans are obviously the source of the volatile acids, furfural and other furane products, and cellulose would be transformed under similar treatment as that of the pentosans into the acidic substances and, furfural & its derivatives.² Simple sugars and sucrose which would undergo analogous chemical changes by distillation as cellulose and hemicellulose, and are supposed to yield compounds mentioned above.

However, the alkali-soluble constituents of the tars which are obtained from woods and coals, are largely composed of phenolic compounds which are assumed by many chemists to be derived partly from the lignine and partly from carbohydrates, since these compounds and their degradation products occur in these neutral substances, and such an assumption was proved, partly by experiments, to be true. The acidic compounds which were isolated by Masumoto in an impure state from pityrol, should have their origin in the carbohydrates or the protein in the rice bran, since the bran usually lacked lignine and its allied substances.

As a matter of fact, pityrol from commerce and laboratory contains acidic substances in measurable quantity, and this accords with the hypothesis that carbohydrates and protein mostly give rise to acidic substances by distillation.

The distillation of sucrose was undertaken by Hidaka in connection with the explanation of the origin of the alkali-soluble constituents of pityrol.

Sucrose by dry distillation yields tar, an aqueous distillate, charcoal and gas, and the yield of these substances is shown in the table with the results of cellulose as comparison.

	Sucrose	Cellulose ³
Tar & aqueous distillate	25 %	37 %
Charcoal	45 "	34 "
Gas & loss	30 "	29 "

¹ Brenstoff. Chem., **4**, 24 (1924)

² Evidnaun & Schaefer: Ber. D. Chem. Ges., **43**, 2398 (1910)

³ P. Klason, G von Heidenstam, & E. Norlin, Z. angew. Chem., **22**, 1205 (1909)

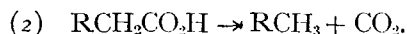
Furfural, methyl furfural & oxymethyl furfural, were found in the distillate and the results are similar to the case of cellulose & glucose.¹

The basic constituents of pityrol which are derived solely from proteins, occur in the bran in accordance with Pictet's suggestion² that protein by dry distillation furnishes the basic compounds together with some organic acids.

According to the experiment by Suzuki, the methyl derivatives of pyridine, quinoline and some aniline were isolated from the basic fraction of pityrol, and it is remarkable that the basic compounds in pityrol are entirely absent from pyrrol & its derivatives, and these facts will suggest that the pyridine bases in the tar would have their origin in pyrrol and its derivatives, and that the former are formed by the pyrogenic reaction from the latter compounds during the destructive distillation.

When rice bran is subjected to dry distillation in a retort, 38% and 30% of the organic substances in the bran were transformed into tar and coke respectively, while with bituminous coal by distillation at 500°, 7% of its organic matter was converted into tar and 70% remained as coke. The yield of the tar from lignine and cellulose which are the chief constituents of wood, was estimated to be 30% and 70% respectively. These facts indicate that the open chain carbon compounds such as fat, & the carbohydrates, give rise to tar in a large amount; and close-chain carbon compound on the contrary yield tar in less quantity than the former compounds.

With regard to the chemical changes which take place in the fatty constituents of rice bran in retort, we can picture to ourselves the probable course as follows:—the primary effect of heat on the fatty acids is to cause an elimination of CO₂ from the molecule in both ways:



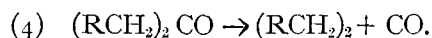
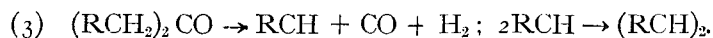
Ketones which are formed from acids by splitting off CO₂ & H₂O, being of unstable nature toward heat³, and will in turn eliminate CO by loosening or dissolving the bonds between the carbon atoms, together with a simultaneous dissociation of hydrogen, giving rise to residues such as RCH₂ or RCH, which may subsequently either form unsaturated compounds by intra-molecular rearrangement or polymerize to form high

1 E. von Lippmann: Die Chemi d. Zuckerarten. I (1904) 301

2 Hel. Chim. Acta, **2**, 188 (1919) and refer the distillation of silk fibroin by Johnson. J. Am. Chem. Soc., **41**, 1147 (1919)

3 P. Sabatier: La Catalyse en chimie organique, 327 (1920)

molecular compounds as indicated below :



Experimental facts accord well with the hypothesis indicated above, in isolating palmitone, saturated & unsaturated hydrocarbons by Shoyama from the distillate of palmitate. The gas evolved from the retort in which palmitic or oleic acids are carbonized at a temperature of 500° , contains equal quantities of CO and CO_2 in both cases, and the result supports the correctness of our hypothesis for the transformation of fatty substances by distillation.

It is, however, surprising that the composition of the gas from rice bran carbonized in the retort, not only differs qualitatively from that of the acids, but quantitatively also, containing comparatively little CO, still less hydrogen and lower members of saturated hydrocarbons, although the CO_2 -content is as high as 32 per cent. Thermal decomposition of carbohydrates & other substances, except of fatty substances occurring in rice bran may account for such an unexpected result.

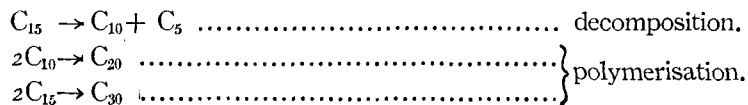
Gas-Analysis

Yield	Rice Bran		Palmitate 6 %	Oleate 18%	Wood —
	A 12%	B 14%			
$\text{C}_n\text{H}_{2n+2}$ & H	2	3	36	46	7
C_nH_{2n}	26	18	29	23	2
CO	17	21	12	15	24
CO_2	32	32	12	16	67

As a consequence, in the case of rice bran, the thermal reaction of its organic substances resulted in the percentage of the olefines in the gaseous product being found to be much higher than the percentage of paraffin & hydrogen, while the decomposition phase of the paraffin hydrocarbons formed from the fatty acids by the primary reaction, which has been described previously, would be the same in both the fatty acids & the rice bran in forming hydrocarbons of low molecular weight.

As a matter of fact, the paraffin hydrocarbons C_9H_{20} , $\text{C}_{10}\text{H}_{22}$, $\text{C}_{15}\text{H}_{32}$, $\text{C}_{30}\text{H}_{62}$ are found in pityrol and also in tars from the fatty acids as a main reaction product, and the facts harmonize with the idea proposed by G. Egloff & R. I. Moore with regard to the thermal stability of the

paraffin hydrocarbons that the hydrocarbons $C_{12}H_{26}$ & $C_{15}H_{32}$ are most stable¹ & those of fewer and of more carbon atoms less stable. Keeping the relative thermal stability of hydrocarbons, which depends on the molecular weight and configuration of the molecule in mind, the thermal changes—decomposition & polymerisation—of the hydrocarbon residue derived by the splitting of the CO_2 from the palmitic & oleic acids, will be interpreted in the following scheme :



To our astonishment, the pathological actions of the constituents of pityrol are quite different in some cases from those of pityrol itself, for instance, the pathological behaviour of the high fraction of the neutral oil from pityrol, which effects on the animal skin to produce cancer is never observed of pityrol or of any fraction of tar derived from palmitic acid.

We are reminded in this connection that Kennaway has expressed his opinion concerning cancer-producing tars, the tar cancer is caused by a very small quantity of an unstable compound that exists in the high-boiling fraction (250° to 500°) of a high temperature coal tar, which will be removed from tar-constituents by purification, as purified anthracene, which, like all other pure compounds does not produce cancer. The cancer-producing principle of the tars, therefore, seems to stand in this respect, in a similar relation as vitamins to food materials.

Such mysterious examples are sometimes noticed in the pharmacological investigations of crude drugs, the action of a crude drug will sometimes diminish markedly or be entirely destroyed on purification or concentration of the active principle by chemical or physical means, due to its partial destruction, disappearance or some other unknown reason by the treatments. The difficulty which has often been encountered in isolating an essence such as an enzyme or a vitamin in a pure state, from natural substances, and the statements which have just been reviewed, give strong support to the belief that the behavior particularly of the biological actions of a compound occurring in nature and isolated in a pure state, towards living organs or substances would not be the same in every respect when it is employed in association with other substances which occur together in nature.

¹ Met. Chem. Eng., 16, 47 (1917)