probably cerotic acid.

4) Acetone-soluble fraction obtained by lithium-acetone method was found to contain $C_{22}$ tetraënoic acid (docosatetraënoic acid) which is responsible for the stimulation of the repair of tuberculous foci. The acetone-insoluble fraction of lithium salts contained hexadecenoic and octadecenoic acids.

5) Glycerol was isolated in the theoretical amount calculated on the basis of triglyceride of $C_{20}$ fatty acid.

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## 39. **Takaaki Aoyagi*** : Studies on the Lipid of *Pelteobagrus nudiceps*. II.[1] The Structure of Octadecenoic Acid and Docosatetraënoic acid isolated from *Pelteobagrus nudiceps*.

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In the preceding paper[1] the active substance that stimulates the repair of tuberculosis foci in guinea pig was shown to be docosatetraënoic acid, $C_{22}H_{36}O_2$. The present paper deals with the chemical structure of this acid. The structure of octadecenoic acid, which occupied the major part of the fatty acids of *Pelteobagrus nudiceps*, was also determined.

Ozonolysis[2~5] was carried out in the determination of both acids. In order to avoid polymerization or the production of peroxide, ozone was saturated at a low temperature (at −10°) and to avoid polymerization of aldehyde in the oxidation products, oxidation with hydrogen peroxide after the decomposition of ozonide was also carried out at a low temperature.

Following the above-mentioned procedures, acids separated and isolated after the oxidation were identified as their anilide, amide, *p*-bromophenacyl ester, and by other physical properties.[6~8]

After ozonolysis of methyl octadecenoate and steam distillation of the products, pelargonic acid, $C_9H_{18}O_2$, was identified in the distillate. After saponification of the residue of steam distillation, azelaic acid, $C_9H_{16}O_4$, was isolated and identified. Therefore, for the octadecenoic acid obtained from the lipid of this fish a structure of 9-octadecenoic acid is proposed. This acid is assumed to be oleic acid rather than elaidic acid from its physical constants.

During the ozonolysis of methyl docosatetraënoate, carbon dioxide and acetaldehyde were found in the volatile fraction and after subsequent oxidation with peroxide, acetic acid and caproic acid were isolated from the distillate. The residue from the distilla-

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* This work was carried out while the author maintained the scholarship given by Kamakura Institute of Tuberculosis.

** Chojamaru, Kamiohsaki, Shinagawa-ku, Tokyo (青柳高明).

1) T. Aoyagi : This Bulletin, 5, 224(1957).
2) Y. Toyama, *et al.* : Bull. Chem. Soc. Japan., **10**, 192(1935).
3) D.T. Mowry, *et al.* : J. Biol. Chem., **142**, 679(1942).
4) C.L. Arcus, *et al.* : Biochem. J. (London), **37**, 1(1943).
5) Y. Toyama, *et al.* : Bull. Chem. Soc. Japan, **10**, 411(1935).
6) K.S. Markley : "Fatty Acids," Interscience Publishers, Inc., New York, 322(1947).
7) A.W. Ralston : "Fatty Acids and Their Derivatives," Armour and Company, 81(1948).
8) H.J. Deuel : "The Lipids," Interscience Publishers, Inc., New York, 31(1955).

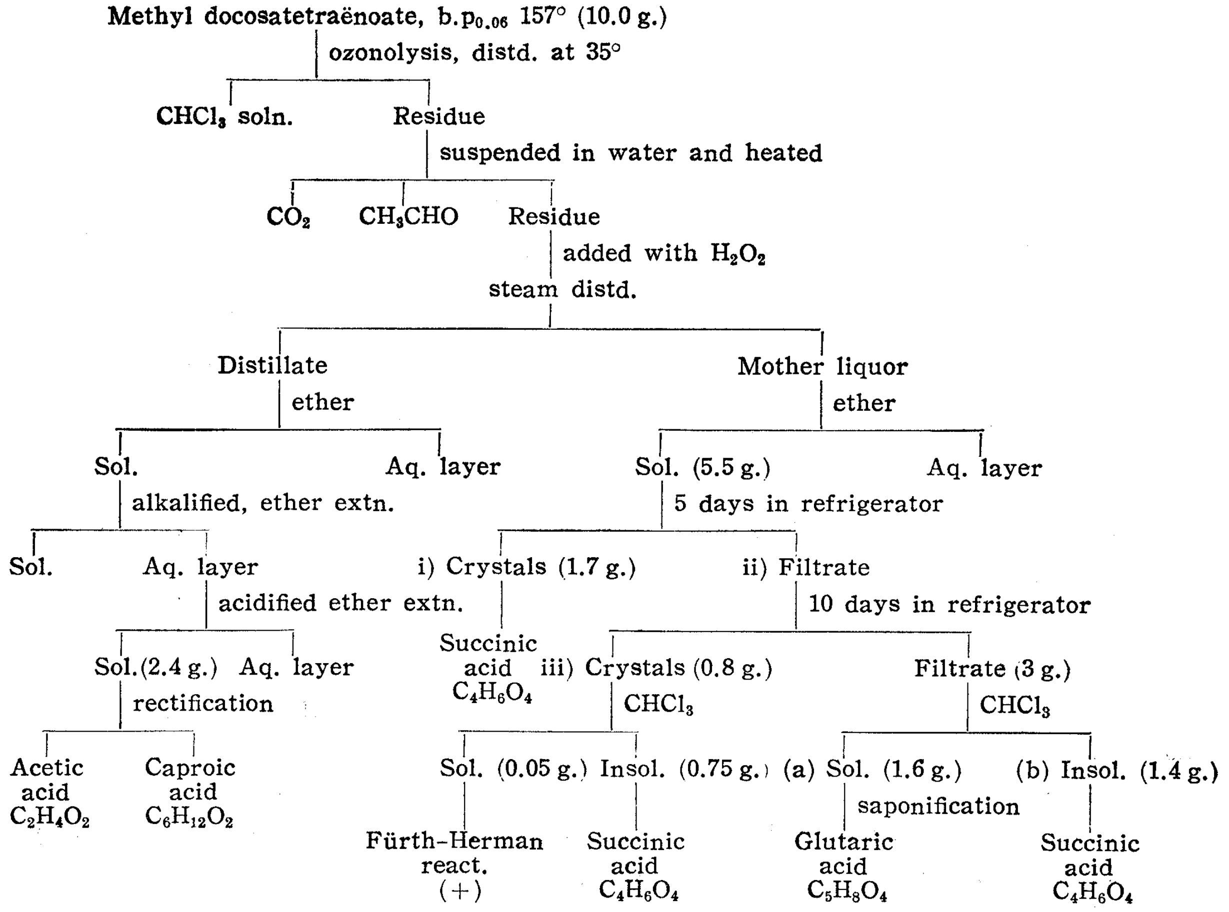

Chart 1. Separation of Oxidative Degradation Products of Methyl Docosatetraënoate

tion gave a relatively large amount of succinic acid and methyl hydrogen glutarate. Carbon dioxide and acetic acid must have been produced by decomposition of malonic acid during ozonolysis$^{3\sim5)}$ because acetone was not detected in the volatile fraction.

The trace of acetaldehyde in the volatile fraction must have been produced by decarboxylation of malonic semialdehyde which was present in a small amount in the degradation products before peroxide oxidation. Therefore, malonic acid is one of the components of the oxidative degradation products.

The yield of these fragments isolated from 10 g. of original acid was as follows:

| Product | Weight (g.) | Mol. yield |
|---|---|---|
| Acetaldehyde | trace | |
| Acetic acid | 0.12 | 0.06 |
| Carbon dioxide | 0.48 | 0.38 |
| Caproic acid | 1.55 | 0.46 |
| Succinic acid | 3.95 | 1.20 |
| Glutaric acid | 1.5 | 0.40 |

The isolation of caproic acid indicates that the terminal double bond is at 15∼16 and the presence of $=CH\cdot(CH_2)_4\cdot CH_3$ moiety. The presence of malonic acid indicates the presence of structure $=CH\cdot CH_2\cdot CH=$. The isolation of large amount of succinic acid indicates that two fragments of $=CH\cdot(CH_2)_2\cdot CH=$ should be involved in the original acid. Glutaric acid isolated after the saponification of semi ester indicated the presence of a terminal group $=CH\cdot(CH_2)_3\cdot COOH$.

In view of the fragments obtained above, three kinds of structure can be proposed for the docosatetraënoic acid.

(I) $CH_3\cdot(CH_2)_4\cdot CH=CH\cdot CH_2\cdot CH=CH\cdot(CH_2)_2\cdot CH=CH\cdot(CH_2)_2\cdot CH=CH\cdot(CH_2)_3\cdot COOH$

(II) $CH_3{\cdot}(CH_2)_4{\cdot}CH{=}CH{\cdot}(CH_2)_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}(CH_2)_2{\cdot}CH{=}CH{\cdot}(CH_2)_3{\cdot}COOH$

(III) $CH_3{\cdot}(CH_2)_4{\cdot}CH{=}CH{\cdot}(CH_2)_2{\cdot}CH{=}CH{\cdot}(CH_2)_2{\cdot}CH{=}CH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}(CH_2)_3{\cdot}COOH$

The final confirmation of these alternatives could not be made, because of the small amount of the material available and unstability of the acid. Moreover, as was stated in the preceding paper,[1] the slight possible contaminants such as trienoic or pentaënoic in this sample can not be completely excluded so far as the present method is concerned. These three structures proposed differ from each other in the distribution of partial structures $=CH{-}CH_2{-}CH=$ and two $=CH{\cdot}(CH_2)_2{\cdot}CH=$ in the whole molecule. Table I[9~14] shows the sequence and position of double bonds in $C_{20}$ and $C_{22}$ straight-chain, unsaturated fatty acids so far reported, especially those with more than four double bonds. As shown by the asterisk marks in Table I, $C_3$ fragment is present adjacent to the sixth or seventh carbon from the ω-position. Therefore, the position of the partial structure $=CH{\cdot}CH_2{\cdot}CH=$ is commonly observable at $C_{14}$–$C_{16}$ or $C_{13}$–$C_{15}$ in $C_{22}$-acids.

TABLE I. Sequence of Double Bonds in $C_{20}$ and $C_{22}$ Unsaturated Fatty Acids

| No. of carbon atoms | Origin | Position of double bonds | Reference |
|---|---|---|---|
| 22 | *Pelteobagrus nudiceps* | $C_6{=}\overset{*}{C}_3{=}C_4{=}C_4{=}C_4{\cdot}COOH$ | |
| | | $C_6{=}C_4{=}C_3{=}C_4{=}C_4{\cdot}COOH$ | |
| | | $C_6{=}C_4{=}C_4{=}C_3{=}C_4{\cdot}COOH$ | |
| | Sardine oil and various kinds of marine animal oil | $C_3{=}C_4{=}\overset{*}{C}_3{=}C_4{=}C_4{=}C_3{\cdot}COOH$ | (8), (14) |
| | Brain | $C_6{=}\overset{*}{C}_3{=}C_3{=}C_6{=}C_3{\cdot}COOH$ | (10) |
| | 〃 | $C_6{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_3{=}C_3{\cdot}COOH$ | (10) |
| | Liver and brain | $C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_6{\cdot}COOH$ | (11) |
| | 〃 | $C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_3{=}C_3{\cdot}COOH$ | (10), (11) |
| 20 | Liver and brain | $C_9{=}C_3{=}C_3{=}C_4{\cdot}COOH$ | (11) |
| | 〃 | $C_6{=}\overset{*}{C}_3{=}C_3{=}C_7{\cdot}COOH$ | (11) |
| | Brain, liver, and suprarenal | $C_6{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_4{\cdot}COOH$ | (6), (7), (9), (11), (12) |
| | Liver and brain | $C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_7{\cdot}COOH$ | (11) |
| | Liver | $C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_4{\cdot}COOH$ | (11) |
| | Brain | $C_7{=}\overset{*}{C}_3{=}C_3{=}C_6{\cdot}COOH$ | (9) |
| | 〃 | $C_7{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_3{\cdot}COOH$ | (9) |
| | 〃 | $C_4{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_6{\cdot}COOH$ | (9) |
| | 〃 | $C_4{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_3{\cdot}COOH$ | (9) |
| | 〃 | $C_1{=}C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_6{\cdot}COOH$ | (9) |
| | 〃 | $C_1{=}C_3{=}C_3{=}\overset{*}{C}_3{=}C_3{=}C_3{=}C_3{\cdot}COOH$ | (9) |
| | Sardine oil | $C_4{=}C_4{=}C_4{=}C_4{=}C_3{\cdot}COOH$ | (12) |
| | 〃 | $C_2{=}C_3{=}C_3{=}C_4{=}C_4{=}C_3{\cdot}COOH$ | (13) |

If this regularity is maintained in natural products, and could be used as an analogy in the docosatetraënoic acid isolated this time, the structure (I) should be the most probable among the three alternatives proposed above. However. these three kinds of structure remain to be confirmed decisively later.

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9) E. Klenk, *et al.* : Z. physiol. Chem., **291**, 104(1952).
10) *idem.* : *Ibid.*, **299**, 74(1955).
11) *idem.* : *Ibid.*, **300**, 113(1955).
12) *idem.* : *Ibid.*, **301**, 156(1955).
13) Y. Toyama, *et al.* : Bull. Chem. Soc. Japan, **10**, 296(1935).
14) Y. Toyama. *et al.* : *Ibid.*, **10**, 301(1935).

Highly unsaturated fatty acids around $C_{20}$ and $C_{22}$ so far reported do not contain either of these three acids now proposed. Hence the chemical constitution of these three docosatetraënoic acid now proposed is a new structure.

The author is indebted to Dr. S. Shoyama, Director of Kamakura Institute of Tuberculosis, for constant encouragement and to Dr. D. Mizuno, Chief of Department of Chemistry, National Institute of Health, and Assist. Prof. T. Ukita, Institute for Infectious Diseases, for their kind advices and suggestions in carrying out the present work. He is also indebted to Misses Ohta, Kondo, and Hara and to Mr. Kurihara for elemental analyses.

## Experimental

**Separation of Oxidative Degradation Products of Methyl Octadecenoate**—Methyl octadecenoate, b.$p_{0.05}$ 124°, iodine no. 83.8, as described in the preceding paper,[1] was used in this experiment. Ten g. of the sample was dissolved in 100 cc. of $CHCl_3$. The solution was chilled to $-10°$ with ice-salt bath and saturated with ozonized oxygen. The solvent was distilled off to leave the ozonide as a light yellow syrup. The yield of the ozonide thus obtained was 12.7 g. 100 cc. of water was added to the ozonide and heated in a water bath for 1 hr., introducing $CO_2$-free $N_2$ gas in the solution but no $CO_2$ or acetaldehyde was found in the trap. 30% $H_2O_2$ solution was slowly added to the above solution until negative to Schiff test and the mixture was heated for over 1 hr. The solution was then steam-distilled to be separated into a distillate (a) and residue (b).

Steam distillate was extracted with ether by continuous extractor, giving 4.6 g. (neutral. equiv. 260.0) of oil which was subjected to rectification and divided into 4 fractions.

| Fraction No. | b.$p_{19}$ | Yield (g.) | Neutral equiv. |
|---|---|---|---|
| I | ~129 | 0.6 | 137.1 |
| II | 130~135 | 1.8 | 340.0 |
| III | 136~140 | 1.6 | 345.2 |
| IV | residue | 0.6 | |

Fractions II and III showed nearly the same neutralization equivalent and these fractions were combined and redistilled to afford an oil, b.$p_{19}$ 130~135°, neutralization equivalent 342.8. *p*-Bromophenacyl ester, m.p. 61.5~62.5°. *Anal.* Calcd. for $C_{17}H_{23}O_3Br$ : C, 57.46; H, 6.48. Found : C, 57.43; H, 6.48. Amide, m.p. 95~96°. *Anal.* Calcd. for $C_9H_{19}ON$ : C, 68.74; H, 12.18; N, 8.91. Found : C, 69.12; H, 11.81; N, 8.73. No depression of the melting point was observed on admixture of the acid and its derivatives with authentic pelargonic acid and its *p*-bromophenacyl ester and amide.

The residue was saturated with NaCl and repeatedly extracted with ether, giving 5.0 g. of a solid material, which was saponified with 1.5*N* ethanolic KOH. The non-saponifiable substance was removed with ether and the aqueous solution was acidified with HCl, saturated with NaCl, and extracted with ether. On removal of the solvent 4.6 g. of white crystals were obtained. Recrystallization from hot water gave white crystals, m.p. 103~104°, neutral. equiv. 598.2, which gave a *p*-bromophenacyl ester, m.p. 128~129° (*Anal.* Calcd. for $C_{25}H_{26}O_6Br_2$ : C, 51.55; H, 4.47; Br, 27.49. Found : C, 51.83; H, 4.72; Br, 27.20) and an anilide, m.p. 182~183° (*Anal.* Calcd. for $C_{21}H_{26}O_2N_2$ : C, 74.52; H, 7.74; N, 8.28. Found : C, 74.37; H, 7.71; N, 8.03). No depression of the melting point was observed on admixture of the acid and these derivatives with authentic azelaic acid and its *p*-bromophenacyl ester and anilide.

**Separation of Oxidative Degradation Products of Methyl Docosatetraënoate**—Ten g. of methyl docosatetraënoate (b.$p_{0.05}$ 157°, iodine no. 278.1) was dissolved in 150 cc. of $CHCl_3$, the solution was chilled to $-10°$ in ice-salt bath, and saturated with ozonized oxygen. The solvent was removed by distillation at 35° and the ozonide was obtained as a light yellow syrup (yield, 23.0 g.). Since the ozonide was highly unstable and there was a danger of explosive decomposition on undue heating, $CHCl_3$ was not thoroughly distilled off, thus the ozonide obtained above retained some $CHCl_3$. 200 cc. of water was added to the ozonide and the solution was placed in a four-necked flask provided with a mercury-sealed stirrer, an inlet tube for a slow bubbling of $CO_2$-free nitrogen gas, a dropping funnel, and a reflux condenser leading in succession to dry-ice cooled traps (a), drierite tube (b), and natron asbestos (c). While vigorously stirring and heating, the aqueous suspension was maintained for 1.5 hrs., the volatile substances (A) formed by the decomposition of ozonide carried over with $N_2$ gas into three apparatus (a, b, and c).

After the solution was cool, 30% $H_2O_2$ was slowly added through the dropping funnel until the solution became negative to the Schiff test and heating was continued for more than 1 hr. The solution was then distilled with steam to separate into a distillate (B) and residue (C).

A) Volatile product : The solution in the dry-ice traps (a) gave pink coloration with the Schiff reagents and deep blue coloration with diethylamine and sodium nitroprusside, indicating the presence of an aldehyde. Its 2,4-dinitrophenylhydrazone could not be purified due to a poor yield. This although it could not be identified, should be acetaldehyde, produced by decarboxylation of malonic semialdehyde. The weight of natron asbestos (c) was found to be increased by 0.48 g., indicating that carbon dioxide was formed by the ozonolysis of methyl docosatetraënoate.

B) Products obtained from the steam distillate: Steam distillate was saturated with NaCl and extracted with ether, giving 3.0 g. of a light yellow oil which still colored slightly pink with Schiff's reagent. This oil was again dissolved in carbonate solution and extracted with ether, a yellow oily product obtained from ether layer (yield, 0.4 g.) gave pink coloration with Schiff's reagent and its aldehydes which remained unoxidized with peroxide. The aqueous solution was acidified with HCl, saturated with NaCl, and extracted with ether, yielding 2.4 g. of light yellow oil. The oil was subjected to fractional distillation and divided into the following 6 fractions:

| Fraction No. | b.p. (°C/mm. Hg) | Yield (g.) | Neutral. equiv. |
|---|---|---|---|
| I | 45/100 | 0.12 | 948.9 |
| II | 100/15 | 0.1 | — |
| III | 103～105/15 | 1.05 | 470.6 |
| IV | 106～108/15 | 0.45 | 423.0 |
| V | 109～110/15 | 0.05 | 382.3 |
| VI | residue | 0.55 | |

Fraction I, b.p$_{100}$ 45°, formed a *p*-bromophenacyl ester, m.p. 84.5～85°. *Anal.* Calcd. for $C_{10}H_9O_3Br$: C, 46.69; H, 3.50. Found: C, 46.58; H, 3.64. No depression of the melting point was observed when the sample was mixed with authentic specimen of *p*-bromophenacyl ester of acetic acid.

Fraction III, b.p$_{15}$ 103～105°, gave an anilide, m.p. 92～93°. *Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.96; H, 9.06; N, 7.23. No depression of the melting point was observed when the sample was mixed with authentic specimen of anilide of caproic acid.

Fraction IV which showed about the same boiling point and neutralization equivalent as those of fraction III gave an anilide of m.p. 90～91°, showing no depression of the melting point when mixed with authentic specimen of anilide of caproic acid.

C) Products obtained from the residue of steam distillation: Steam distillation residue was saturated with NaCl and the solution repeatedly extracted with ether, giving 5.5 g. of a slightly yellow oily substance which was allowed to stand in a refrigerator for 5 days to separate a solid substance. The solid material thus separated was filtered (yield 1.7 g.) (i), which showed neutralization equivalent of 922.3. (see Fig. 1)

(i) This product was negative to Fürth-Herman reaction.[15] Recrystallization from AcOEt gave white prisms, m.p. 181.5～182.5°, neutralization equivalent 945.2. *Anal.* Calcd. for $C_4H_6O_4$: C, 40.68; H, 5.12; COOH, 76.27. Found: C, 40.61; H, 5.10; COOH, 76.76. *p*-Bromophenacyl ester, m.p. 208～209°. *Anal.* Calcd. for $C_{20}H_{16}O_6Br_2$: C, 46.88; H, 3.13. Found: C, 46.93; H, 3.17. No depression of the melting point was observed on admixture of the acid and its *p*-bromophenacyl ester with authentic specimen of succinic acid and its *p*-bromophenacyl ester.

(ii) The filtrate was allowed to stand in a refrigerator for 10 more days and a solid was separated. 0.8 g. of a crystalline material (iii) was separated by filtration, leaving 3.0 g. of an oily substance. The oily portion was extracted with $CHCl_3$ to be divided into two fractions, $CHCl_3$-soluble, slightly yellow syrup (1.6 g.) (a) and an insoluble white prisms (1.4 g.) (b) (see Chart 1).

a) $CHCl_3$-soluble fraction (neutral. equiv. 510.1) was saponified with ethanolic KOH. The non-saponifiable substance was removed with ether (yield, 0.05 g.), which was not examined further. The saponified solution was acidified with HCl, saturated with NaCl, and extracted with ether. On removal of the solvent 1.55 g. of white crystals with neutralization equivalent of 879.6 was obtained. It was again extracted with $CHCl_3$ by Soxhlet apparatus to give 1.5 g. of white crystals, which were recrystallized from benzene to yield white prisms, m.p. 91.5～92.5°(neutral. equiv. 831.5). *Anal.* Calcd. for $C_5H_8O_4$: C, 45.45; H, 6.10. Found: C, 45.89; H, 5.95. *p*-Bromophenacyl ester, m.p. 132～133°. *Anal.* Calcd. for $C_{21}H_{18}O_6Br_2$ C, 47.90; H, 3.42. Found: C, 47.55; H, 3.13. No depression of the melting point was observed on admixture of the acid and its *p*-bromophenacyl ester with authentic specimens of glutaric acid and its *p*-bromophenacyl ester.

b) The $CHCl_3$-insoluble fraction (1.4 g.) was recrystallized from AcOEt to white prisms, m.p. 180～181°, neutral. equiv. 921.5. No depression of the melting point was observed when the sample was mixed with the authentic sample of succinic acid.

This substance (iii) (0.8 g.) showed positive Fürth-Herman reaction (cf. Chart 1). It was treated with $CHCl_3$ to separate into $CHCl_3$-soluble and -insoluble parts. Soluble fraction (50 mg., neutral. equiv. 1060.0) was recrystallized from AcOEt to give a few mg. of white crystals, m.p. 120～128°. Though this substance was not obtained in a pure state, it will be presumed that this product is malonic acid from its neutral. equiv. 1060.0 (Calcd. for malonic acid, 1078.5) and the positive Fürth-Herman

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15) Funakubo: "Yūkikagobutsu Kakuninhō," II, 3(1953).

reaction.

$CHCl_3$-insoluble crystals (0.75 g.) were recrystallized from AcOEt to white prisms, m.p. 180~181°, neutral. equiv. 931.5. No depression of the melting point was observed on admixture with an authentic sample of succinic acid.

## Summary

1) Octadecenoic acid obtained from the lipid of *Pelteobagrus nudiceps* was determined as $CH_3\cdot(CH_2)_7\cdot CH{=}CH\cdot(CH_2)_7\cdot COOH$ by ozonolysis.

2) The structure of docosatetraënoic acid isolated from *Pelteobagrus nudiceps* and responsible for stimulation of the repair of tuberculous foci was proposed as

$$CH_3\cdot(CH_2)_4\cdot CH{=}CH\cdot CH_2\cdot CH{=}CH\cdot(CH_2)_2\cdot CH{=}CH\cdot(CH_2)_2\cdot CH{=}CH\cdot(CH_2)_3\cdot COOH.$$

Two other structural possibilities of this acid, with the double bonds in 5–6, 9–10, 12–13, 16–17, or 5–6 8–9, 12–13, 16–17 were not excluded as shown in the discussion.

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*U.D.C. 547.852.07*

## 40. **Noboru Takahayashi**: Synthesis of Pyridazine Derivatives. VIII.* Nucleophilic Substitution of 3,6-Dichloro-4-methylpyridazine.

(*Pharmaceutical Faculty, University of Toyama***)

In the reaction of 3,6-dichloro-4-methylpyridazine (I) and hydrazine hydrate, it was reported by Kubota *et al.*[1] that the melting point of the resulting product was 193°. The author has, however, previously obtained a compound of m.p. 149° by the same reaction and the compound was converted to tetrazolo[4,5-*b*]pyridazine and *s*-triazolo-[4,3-*b*]pyridazine by the action of nitrous acid, formic acid, and acetic anhydride.[2] The methylation of monothiol compound, which was obtained from (I) and potassium hydrogen sulfide, produced 3-chloro-6-methylthio-4(or 5)-methylpyridazine, m.p. 103.5°, and the material was then oxidized.[3]

This paper deals with determination of the position of the methyl groups of those compounds.

The 4(or 5)-methylpyridazine derivatives were prepared by the method of Druey.[4] That is, methylglyoxal which was obtained by the oxidation of acetone with selenium dioxide was condensed with cyanoacetohydrazide, and the resulting mixture of 5-methyl and 6-methyl compounds was separated by crystallization from chloroform and benzene. Each of those products was hydrolysed and decarboxylated, producing 5-methyl-3-pyridazinol (IIIb) and 6-methyl-3-pyridazinol (IIIc), respectively. (IIIc) was identical with the sample prepared from ethyl levulate and hydrazine hydrate by the method reported in the first paper of this series.[5]

Saponification of (I) by heating with 15% sodium hydroxide gave the mixture of (IIa) (needles, m.p. 148°, 75~80%) and (IIb) (leaflets, m.p. 227°, 15~20%). The latter was less soluble than the former in methanol and they could be separated by fractional recrystal-

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* Part VII: J. Pharm. Soc. Japan, **76**, 1296(1956).

** Okuda Toyama (高林 昇).

[1] H. Kubota, *et al.*: The 74th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April, 1954.

[2] N. Takahayashi: J. Pharm. Soc. Japan, **75**, 1242(1955).

[3] *Idem.*: *Ibid.*, **75**, 1245(1955).

[4] P. Schmidt, J. Druey: Helv. Chim. Acta, **37**, 1467(1954).

[5] D. Shiho, N. Takahayashi: J. Pharm. Soc. Japan, **75**, 776(1955).