zation from acetone, an acid melting at 217–218.5° is obtained. This substance has the same data as 2,3-dimethoxy-diphenyl ether-5,4'-dicarboxylic acid which Faltis¹⁰⁾ once derived from methyl 3-hydroxy-4,5-dimethoxy-benzoate and methyl 4-bromo-benzoate.

2,6-Dimethoxy-diphenyl ether-4,4'-dicarboxylic acid—0.15 g. of metal potassium are dissolved in 8 cc. of anhydrous methanol, and 0.98 g. of methyl 4-hydroxy-3,5-dimethoxybenzoate¹⁶⁾ in a methanol solution are added, then a colorless potassium salt deposits. The solvent is distilled under reduced pressure, then 0.84 g. of methyl *p*-bromobenzoate, 0.1 g. of copper powder, and 0.1 g. of anhydrous copper acetate are added, and the mixture is heated for 3 hours in an oil bath at 200°. The substance is extracted with warm ether, and after its treatment, a light-orange, crystalline substance containing oily matter is gained. By its vacuum distillation, unreacted methyl *p*-bromobenzoate distills out at first, and the compound does not distill even at 200° (2 mm.). Then, by recrystallization of the distillation residue from methanol and ether, almost colorless, prismatic crystals of m.p. 147–148° are obtained.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24. Found C, 62.89; H, 5.50.

When the acid, gained by the saponification of the ester with a *N*-alcoholic potassium hydroxide solution, is recrystallized from ether, colorless, minute crystals of m.p. 251–252° are deposited.

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.33; H, 4.43. Found C, 60.29; H, 4.53.

Summary

The structure of magnoline and magnolamine, two alkaloids from the leaves of *Magnolia fuscata*, were reexamined. The tentative structure of dauricine type, proposed by Proskurnina, was examined through oxidation product of the two alkaloids, magnolamic acid, or dimethoxydiphenyl ether-dicarboxylic acid. For its determination, 2,3-dimethoxy-diphenyl ether-5,4'-dicarboxylic, 2,6-dimethoxydiphenyl ether-4,4'-dicarboxylic acids were synthesized but neither compound coincided with magnolamic acid.

100. Tatsuo Moroe*: Studies of Phthioic Acid. VIII.

A New Synthesis of 3,13,19-Trimethyltricosanoic Acid¹⁾

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Liquid, saturated fatty acid, phthioic acid, an isomer of cerotic acid, $C_{26}H_{52}O_2$, was first isolated by Anderson²⁾ from the mixed liquid saturated acids obtained through hydrolysing the phosphatides of the human tubercle bacilli, and was also found by Chargaff and Anderson³⁾ in the acetone-soluble fat of the same bacillus in large portions. On the physiological activity of this acid Sabin and his associates⁴⁾ reported that on injecting into normal animals the acid stimulated proliferation of monocytes, epithelioid

16) Bogert and Ehrlich: J. Am. Chem. Soc. **41**, 800; Greabe and Martz: Ber., **36**, 217.

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1) Synthesis of Branched-Chain Fatty Acids Present in Tubercle Bacillus. X, reported at the monthly meeting of the Pharmaceutical Society of Japan, October 17, 1949, in Tokyo.

Part I: Asano, Kameda and Wada: This Journal, **63**, 538 [1943]; Part II, III, Reference (15); Part IV, V, Reference (16).

2) Anderson: J. Biol. Chem., **74**, 537 [1927]; ibid. **83**, 169 [1929].

3) Anderson and Chargaff: J. Biol. Chem. **85**, 77 [1929–1930].

4) Sabin: J. Exper. Med., **52**, Suppl. **3**, 3 [1930]; **61**, 771 [1935]; Physiol. Rev., **12**, 141 [1932].

and giant cell with the formation of typical tubercular tissue. So it has been a problem of great interest to decide the chemical structure of this acid.

Many investigations on the structure of this acid have recently been reported by Anderson,⁵⁾ Chargaff,⁶⁾ Spielman and Anderson,⁷⁾ Wagner-Jauregg,⁸⁾ Robinson,⁹⁾ Stenhagen and Ställberg,¹⁰⁾ Birch and Robinson,¹¹⁾ Schneider and Spielman,¹²⁾ Cason,¹³⁾ and Bun Hoi and Cagniant.¹⁴⁾ Among them, Stenhagen and Ställberg suggested that phthioic acid might be a trialkyl-substituted acetic acid on the basis of the properties of surface films and X-ray examination of its barium salt. As the most possible of the formulae suggested by Stenhagen and Ställberg, ethyl-decyl-dodecyl-acetic acid ($C_{26}H_{52}O_2$) was first proposed by Robinson.⁹⁾ However, subsequent investigations yielded evidence that the above structure was incorrect. Following the suggestion of Robinson, Asano and co-workers^{15,16)} synthesized a series of trialkyl-substituted acetic acid, introduced alkyl-groups such as ethyl-*n*-decyl-*n*-dodecyl, methyl-*n*-undecyl-*n*-dodecyl and ethyl-*n*-nonyl-*n*-dodecyl, and found that the saponification velocity of the synthesized esters was by far slower than that of the natural phthioic acid. Also, the same author in collaboration with Yamagiwa et al.,¹⁷⁾ found that the cellular reactions by the injection of ethyl-nonyl-dodecyl-acetic acid in rabbits differed much from those of tubercle bacillus and its phosphatide. These facts led them to take different views on the structure of phthioic acid, contrary to the previously mentioned formula. Isawa¹⁸⁾ also reported the same conclusion from the results of the surface film examination of trialkylacetic acids which were synthesized by Asano, et al.

Polgar and Robinson¹⁹⁾ reported that the properties of surface film of trialkylacetic acid, which was previously suggested, differed from those of natural phthioic acid. Phthioic acid gives mono-layers which collapse by compression at $39 \text{ \AA}^2$, and this minimum area is fairly comparable with that of the compressed normal chain acid, while monolayers of trialkylacetic acids collapse at $62 \text{ \AA}^2$. They also reported that 2,13,17,21-tetramethyldocosanoic acid has the monolayers most similar to those of phthioic acid which has a limiting area of $61 \text{ \AA}^2$, and no collapsing at $39 \text{ \AA}^2$ by compression, and the methyl group in the 21st position has no effect upon the minimum area of the film, and that structure of undecoic acid which can be obtained by oxidizing phthioic acid⁷⁾ is 6-methyl-decoic acid.

From above reasons and the fact that Wagner-Jauregg⁸⁾ obtained azelaic acid from the oxidation product of phthioic acid, they suggested that phthioic acid should have a chemical configuration of 3,13,19-trimethyltricosanoic acid (I).

5) Anderson : J. Biol. Chem., **97**, 639 [1932].

6) Chargaff : Ber., **65**, 745 [1932].

7) Spielman and Anderson : J. Biol. Chem., **112**, 759 [1935-1936].

8) Wagner-Jauregg : Z. physiol. Chem., **247**, 135 [1937].

9) Robinson : J. Chem. Soc., 505 [1940].

10) Stenhagen and Ställberg : J. Biol. Chem., **139**, 345 [1941].

11) Birch and Robinson : J. Chem. Soc., 488 [1942].

12) Schneider and Spielman : J. Biol. Chem., **142**, 345 [1942].

13) Cason : J. Am. Chem. Soc., **64**, 1106 [1942].

14) Bun Hoi and Cagniant : Z. physiol. Chem., **279**, 761 [1943]; Ber. **76**, 689 [1943].

15) Asano, Kameda and Wada : This Journal, **64**, 125 [1944].

16) Asano, Kameda and Wada : This Journal, **65**, 415 [1945]; Igakusoran **2**, 54 [1945].

17) Asano and Yamagiwa : Igakusoran, **2**, 51 [1945].

18) Isawa : This was reported at the monthly meeting of the Chemical Society of Japan, April 1947, in Tokyo.

19) Polgar and Robinson : J. Chem. Soc., 615 [1943].

Then, Polgar and Robinson's splendid idea was confirmed by the synthesis of 3,13,19-trimethyltricosanoic acid and it exhibited all the characters and behaviors of the natural phthioic acid.²⁰⁾

On the other hand, Wilson²¹⁾ published the same structure (I) independently on the basis of another view point. He determined the structure of the eleven-membered fatty acid which was produced by the oxidation of phthioic acid through synthetically identifying it as 6-methyldecoic acid. Wagner-Jauregg showed phthioic acid to possess three or four methyl groups as side chains which were analyzed by the method of Kuhn-Roth, and also isolated aszelaic acid, though phthioic acid has a high optical rotatory power.

Thus, for these reasons, it seems rather preferable to stand for Wilson's view point than the Robinson's.

However, 3,13,19-trimethyltricosanoic acid was not synthesized by Wilson.

The formula (I) agrees with experimental results of Spielman and Anderson⁷⁾ who asserted that phthioic acid should be a branched, long chain acid with methyl groups as side chains.

Later, Cason and Prout²²⁾ pointed out that the formula (I) is not complete enough to explain the fact that phthioic acid has a high molecular rotation, and they discussed that 2,3,21-trimethyltricosanoic acid may be just the best compatible one with phthioic acid from the view-point of optical rotation, although 2,3,21-trimethyltricosanoic acid formula cannot explain the formation of 6-methyldecoic acid by the oxidation of phthioic acid.

Thus, in view of above evidences, it seems undoubted that phthioic acid has the structure suggested by Polgar and Robinson.

Thereupon, the author synthesized 3,13,19-trimethyltricosanoic acid by another procedure than that mentioned by Polgar and Robinson. In the present paper is reported the experimental course of this synthesis. For comparison, Polgar and Robinson's method is shown as follows.

20) Polgar and Robinson : J. Chem. Soc., 389 [1945].

21) Wilson : J. Am. Chem. Soc., **67**, 2161 [1945].

22) Cason and Prout : J. Am. Chem. Soc., **70**, 879 [1948].

There are some difficulties in Polgar and Robinson's synthesis, viz., in the course of addition of HI to omega-double bond position of (IV), if oxygen or oxygen-effect substance is absent, (V) is mainly produced, but simultaneously, a small amount of (VI) is formed, and the distinct separation of these two iodides from each other is very difficult. Therefore, in order to obtain pure (I) free from undesirable impurities, the author devised a means to synthesize (I) by a more simple procedure which involves the condensation of 6-methyldecoic acid and monoester of 2,12-dimethyl-tridecane-1,13-dicarboxylic acid by Kolbe's electrolysis, as follows :

In this way, $\text{C}_{20}\text{H}_{42}$ (XI) was separated by alkaline solution from the ester of (I) and (XII) through hydrolyzing the reaction product, and they were separated easily from each other through distillation.

6-Methyldecoic acid has previously²⁰⁾²¹⁾ been synthesized from 6-ketocaproic acid or levulic acid. On this occasion, it was synthesized from 6-ketodecoic acid as follows:

Two following processes can be planned for the preparation of 2,12-dimethyltridecane-1,13-dicarboxylic acid (XIX), which has not been synthesized previously.

Process A

Process B

In the previous papers,²³⁾ it was shown that 1,11-dimethyl-dodecane-1,12-dicarboxylic acid, which has one carbon atom less than (XIX) was synthesized in a better yield by the process (B) from sebacic acid than by the process (A) from hexane dibromide. Therefore, (XIX) was prepared by the process (B) from nonane-1,9-dicarboxylic acid.

The acid (I) thus obtained is a pale yellowish, viscous liquid. The physical properties of the acid and the derivatives are shown in Table I, with references to those of the natural phthioic acid and the acid synthesized by Polgar and Robinson.

Table I

	m.p. °C	b.p. °C	n_D	$[\alpha]_D$	Amide, m.p. °C	<i>p</i> -Br-Phenacyl ester m.p. °C
Spielman, Anderson*	20-21		n_D^{25} 1.4628	+12.5°	45	—
Polgar, Robinson		208 (0.1mm)	n_D^{17} 1.4620	—	37	—
Author		205-208 (0.1 mm)	n_D^{17} 1.4600	—	43-44	97-98

* Natural phthioic acid.

As can be seen in Table I, the melting point of the amide approximately coincides with the amide of the natural phthioic acid which was derived by Spielman and Anderson. A new derivative, *p*-bromophenacyl ester as white needles, melting at 97-98°, was obtained by the author.

The formation of *p*-bromophenacyl ester will give a new key to the studies of phthioic acid.

The author is now testing the physiological activity of 3,13,19-trimethyltricosanoic acid synthesized and he is looking forward to the many interesting results which will be reported in the near future.

The author wishes to express his hearty thanks to the late Prof. M. Asano, the former Director of the Department, for his sincere guidance in this work, and to Prof. S. Akiya, the present Director of the Department, and to Dr. T. Ukita, for their kind suggestions. The author's thanks are also due to Dr. T. Hiraizumi, President of the Takasago Chemical Industries Company for his direct encouragements and kindnesses given throughout this research.

Experimental

Ethyl 6-Ketodecoate (VIII)—The free acid was prepared from butylzinc iodide and carbethoxyadipyl chloride by the method used by Ruzicka and Stoll.²⁴⁾ It melted at 45-46° and boiled at 194-195° (7 mm). Yield, 65%. Ethyl ester, prepared by the usual method, boiled at 119-120° (3 mm). Yield, 70%.

6-Methyldecoic Acid (IX)^{20,21)}—This was synthesized from methylzinc iodide and ethyl 6-ketodecoate in the same way as was used by Polgar and Robinson. The yield of the acid was 41% of ethyl 6-ketodecoate. It had a b.p. of 163-164°, and n_D^{20} 1.4360. The

23) Moroe : Studies of Phthioic Acid, VI, VII. Unpublished.

24) Ruzicka and Stoll : Helv. Chim. Acta. **10**, 692 [1927].

melting point of *p*-bromophenacyl ester^{20,21)} was 50.5° and that of tribromoanilide^{20,21)}, 104.5°.

11-Bromoundecoic Acid (XIV)—This was prepared from undecenoic acid and gaseous hydrobromic acid in the presence of air, following the procedure of Ashton.²⁵⁾ The bromo-acid, after recrystallization from benzene-petroleum ether mixture, gave m.p. of 50°.

11-Hydroxyundecoic Acid (XV)²⁵⁾—Quantitatively, 11-bromoundecoic acid was converted to its ethyl ester which boiled at 148–150° (4 mm.). The bromo ester, by the action of potassium acetate and acetic acid, and then hydrolyzed, gave 11-hydroxyundecoic acid. Recrystallized from benzene, it melted at 65–66°. Yield, 65 %.

Nonane-1,9-dicarboxylic Acid (XVI)²⁶⁾—An alkaline solution of 250 g. of 11-hydroxyundecoic acid (XV) was oxidized with 390 g. of potassium permanganate at room temperature for 24 hours. On acidifying the resulting product, the acid was obtained and recrystallized from concentrated nitric acid and then again from boiled water. Yield, 160 g. (68 %). Further crystallization from benzene-ligroin, gave needles which melted at 110–111°.

Nonane-1,9-dicarboxylic Chloride (XVII)—A mixture of 22 g. of nonane-1,9-dicarboxylic acid and 28 g. of thionyl chloride was heated on a water bath at 50° for two hours, and then allowed to stand at 70° for 30 minutes. Unchanged thionyl chloride was removed by distillation under reduced pressure, and the residue distilled in vacuo. The chloride boiled at 156–160° (5 mm.). Yield, 39 %.

Tridecane-2,12-dione (XVIII)²⁸⁾—The synthesis of this ketone followed the method of Blaise and Koehler.²⁷⁾ Methylzinc iodide (prepared from 20 g. of mossy zinc, 42 g. of methyl iodide, 9 g. of ethyl acetate and 18 g. of toluene) was treated with 26 g. of nonane-1,9-dicarboxylic chloride at 0° for 3 hours. The reaction product was decomposed by water, and then the ketone was separated and distilled in vacuo. It boiled at 153–155° (5 mm.). White prismatic crystals, m.p. 72°, were obtained by recrystallization from petroleum ether. Yield, 19 g. (89 % of the chloride).

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.60; H, 11.30. Found: C, 73.90; H, 11.28.

Disemicarbazone, m.p. 197–198°, was prepared in the usual manner.

Anal. Calcd. for $C_{15}H_{30}O_2N_6$: C, 55.20; H, 9.20. Found: C, 55.05; H, 9.53. (The m.p. reported is 183–184°²⁸⁾).

2,12-Dimethyltridecane-1,13-dicarboxylic Acid (XIX)—A mixture of 9 g. of tridecane-2,12-dione, 40 g. of ethyl monoiodoacetate, 12 g. of activated zinc powder and 60 g. of benzene, was heated at 70° for 2 hours and refluxed at 90° for 2 hours. When the reaction product was decomposed with dilute hydrochloric acid, diethyl 2,12-dimethyl-2,12-dihydroxytridecane-1,13-dicarboxylate, a viscous, brown liquid, was separated. By distillation with iodine, it was dehydrated into diethyl 2,12-dimethyltridecadiene-1,13-dicarboxylate, which boiled at 160–170° (0.05 mm.). Yield, 10 g. Ten grams of the unsaturated ester were hydrogenated with platinum oxide and hydrogen to diethyl 2,12-dimethyltridecane-1,13-dicarboxylate, b.p._{0.1} 170–174°, n_D^{20} 1.4655. Yield, 3.2 g. After boiling with alcoholic potash, 14 g. of the ester were converted into 2,12-dimethyltridecane-1,13-dicarboxylic acid. Yield, 8.9 g. (49.7 % of tridecane-1,12-dione). The acid boiled at 202–205° (0.05 mm.) and melted at 60–61°.

Anal. Calcd. for $C_{17}H_{32}O_4$: C, 68.00; H, 10.70; COOH, 30.00. Found: C, 67.80; H, 10.56; COOH, 30.30.

Monoethyl 2,12-Dimethyltridecane-1,13-dicarboxylate (X)—Eight grams of the diethyl ester of the above acid, prepared from 10 g. of the acid, 60 cc. of ethanol, and 15 g. of concentrated sulfuric acid, were hydrolyzed by 150 cc. of ethanol, 1.2 g. of potassium hydroxide and 15 g. of water at 70–80° for 6 hours. Then, on acidifying the alkaline solution, the monoester was separated and distilled in vacuo. It boiled at 184–186° (0.06

25) Ashton: J. Chem. Soc., 1308 [1934].

26) Walker and Lumdsen: J. Chem. Soc., 1191 [1901].

27) Blaise and Koehler: Compt. rend., 148, 489 [1909]; 176, 1148 [1923].

28) v. Braun: Ber., 46, 1791 [1913].

mm.). Yield, 4.5 g. (67 %).

Anal. Calcd. for $C_{19}H_{36}O_4$: COOH, 13.71. Found: COOH, 13.70.

Kolbe's Electrolysis of 6-Methyldecoic Acid and Monoethyl 2, 12-Dimethyltridecane-1, 13-dicarboxylate—The electrolytic cell was a 150 cc. glass beaker which was cooled with ice water. The cathode was a platinum spiral (surface area 1 cm²) and the anode, copper net encircling the cathode. The electrolyte was a mixture of 3.3 g. (1 mol.) of the monoester of (XIX), 2.8 g. (1.5 mol.) of 6-methyldecoic acid (IX), 1.9 g. of potassium carbonate, 20 cc. of distilled water and 20 cc. of ethanol, and the pH of the electrolyte was adjusted so as to remain within the minimum range of 6.8-7.0 by the timely addition of 6-methyldecoic acid.

The electrolysis was carried out under the current density of 0.8 amp/cm², while the electrolyte was so cooled as not to raise the reaction temperature over 30°. As the electrolysis proceeded, the mixture of 7.1 g. of the monoester and 8.5 g. of 6-methyldecoic acid was added during 20 hours in several portions. The resulting neutral product was partially and frequently collected from the reaction mixture. Yield, 12 g. The amount of unreacted acids, which was recovered on acidifying the electrolyte, was 12 g.

3, 13, 19-Trimethyltricosanoic Acid (I)—Twelve grams of the neutral product obtained by the electrolysis were hydrolyzed with alcoholic potash (prepared from 13 g. of potassium hydroxide, 100 cc. of ethanol and 20 cc. of water) on a water bath for 6 hours. Ethanol was evaporated under reduced pressure and 200 cc. of water were added to the residue. The opaque, alkaline solution was extracted by the continuous liquid extractor for 10 hours with a mixture of ether and petroleum ether in order to remove the neutral substances which are not hydrolysed. On acidifying this alkaline solution with sulfuric acid, 6 g. of viscous acid product were separated, which by vacuum distillation, gave 2 following fractions: (1) 2.5 g. of b.p._{0.1} 195-213°; and (2) 2.0 g. of b.p._{0.1} above 213°.

The fraction (1), being further rectified, gave a fraction, b.p._{0.1} 205-208°, and n_D^{18} 1.4600. Yield, 1.4 g. The acid was a pale yellowish, viscous liquid, not solidifying on cooling in the ice-box.

Anal. Calcd. for $C_{26}H_{52}O_2$: C, 78.80; H, 13.10; COOH, 11.39. Found: C, 78.92; H, 12.79; COOH, 11.45.

3, 13, 19-Trimethyltricosanoic Acidamide—This was prepared in the usual manner from the acid chloride. The substance, semicrystalline, melted at 43-44°, and boiled at 245° (0.1 mm.).

Anal. Calcd. for $C_{26}H_{53}NO$: C, 79.00; H, 13.40. Found: C, 79.07; H, 13.40.

***p*-Bromophenacyl Ester of 3, 13, 19-Trimethyltricosanoic Acid**—0.2 g. of the acid were converted into its potassium salt and refluxed on a water bath with less than the equimolecular amount of *p*-bromophenacyl bromide and ethanol. The product, viscous, oily liquid, was cooled in an ice box for a week, then the crystallized substances were collected rapidly by filtration, and recrystallized from methanol, giving needles, m.p. 97-98°.

Anal. Calcd. for $C_{34}H_{57}O_3Br$: C, 68.80; H, 9.61. Found: C, 68.46; H, 9.29.

Summary

(1) The author synthesized 3, 13, 19-trimethyltricosanoic acid which is the most probable formula of phthioic acid present in tubercle bacilli.

(2) The method of synthesis which was taken by the author, the electrolytic condensation of 6-methyldecoic acid and monoester of 2, 12-dimethyltridecane-1, 13-dicarboxylic acid, is more convenient than that of Polgar and Robinson.

(3) The acid synthesized has the following physical constants: b.p._{0.1} 205-208°; n_D^{17} 1.4600. The amide melted at 43-44°.

(4) The author obtained a new derivative, *p*-bromophenacyl ester, melting at 97-98°.

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