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Studies of Thio Acids. VII.[1] The Synthesis of Thiopalmitic Acid and Thiomyristic Acid[*1]

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Thiopalmitic acid, $C_{15}H_{31}COSH$ (m. p. 30.8—31.3°C), and thiomyristic acid, $C_{13}H_{27}COSH$ (m. p. 19.8—20.3°C), were synthesized by the reaction of sodium hydrogen sulfide in ethanol with palmitoyl and myristoyl chlorides respectively. The infrared absorption spectra of thiopalmitic and thiomyristic acids indicate that both acids assumed the thiolic acid form. Dipalmitoyl disulfide (m. p. 76.0—76.5°C) and ethyl palmitate, and dimyristoyl disulfide (m. p. 70.5—71.5°C) and ethyl myristate were isolated as by-products.

Auger et al.[2] reported that the melting point of thiopalmitic acid ($C_{15}H_{31}COSH$) was 71°C, while the melting point of thiomyristic acid ($C_{13}H_{27}$-COSH) was lower than 25°C. On the other hand, in a previous paper of this series,[3] it was reported that the melting point of thiostearic acid was 39.8—40.3°C. Such an irregular relationship between the number of carbon atoms and the melting point in the homologous series of higher aliphatic thio acids seems doubtful considering the fact that, in the series of higher fatty acids having odd or even carbon atoms, the melting point rises monotonically with the increasing number of carbon atoms.

For the purpose of solving the above question and obtaining extensive knowledge of the properties of the above thio acids, the present authors made the synthesis of thiopalmitic and thiomyristic acids by a method different from that of Auger et al. and then studied the properties of these thio acids and by-products.

Palmitoyl or myristoyl chloride prepared from palmitic or myristic acid and thionyl chloride by the usual method was added, drop by drop, to an ethanol solution of sodium hydrogen sulfide (prepared from metallic sodium, absolute ethanol, and hydrogen sulfide) with heating. The resulting solution was acidified to produce the crude product. By the fractional crystallization of the crude product from palmitoyl chloride, thiopalmitic acid was obtained in the form of colorless crystals (m. p. 30.8—31.3°C), together with small amounts of dipalmitoyl disulfide (colorless crystals of m. p. 76.0—76.5°C) and ethyl palmitate. On the other hand, the crude product from myristoyl chloride was divided into an acidic fraction and a neutral fraction. By the fractional crystallization of the acidic fraction, thiomyristic acid was obtained in the form of colorless crystals (m. p. 19.8—20.3°C), together with small amounts of dimyristoyl disulfide (colorless crystals of m. p. 70.5—71.5°C) and ethyl myristate. The neutral fraction was confirmed to consist mainly of ethyl myristate.

The separation of thiopalmitic or thiomyristic acid from the respective by-products was achieved by fractional crystallization from petroleum ether or hexane; it was difficult to achieve it by fractional crystallization from other solvents or by fractional distillation under reduced pressure. The quantities of the by-products depended upon the conditions of the reaction. In particular, the formation of

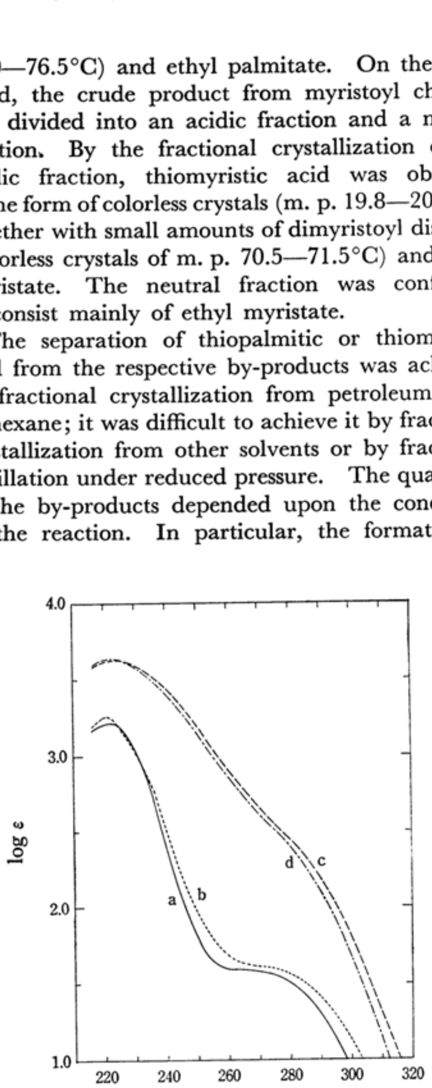

Fig. 1. Ultraviolet absorption spectra in cyclohexane.

a : Thiopalmitic acid c : Dipalmitoyl disulfide
b : Thiomyristic acid d : Dimyristoyl disulfide

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[1] Part VI of this series: Y. Hirabayashi and T. Mazume, This Bulletin, **39**, 1971 (1966).

[*1] Parts of this study were presented at the 11th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1958, and at the Symposium of Oils and Fats of the Chemical Society of Japan, Nagoya, November, 1958.

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[2] V. Auger and M. Billy, *Compt. rend.*, **136**, 555 (1903).

[3] Y. Hirabayashi, M. Mizuta and T. Mazume, This Bulletin, **37**, 1002 (1964).

ethyl palmitate or myristate made the separation of the corresponding thio acid difficult in fractional crystallization. The mechanism of the formation of these by-products may be similar to that of the synthesis of thiostearic acid.³⁾

The ultraviolet absorption spectra of thiopalmitic and thiomyristic acids in cyclohexane solutions*3 are shown in Fig. 1. Thiopalmitic acid shows a band at $\lambda_{max}=221.5\ \text{m}\mu$ ($\varepsilon=1670$), while thiomyristic acid shows a band at $\lambda_{max}=221.0\ \text{m}\mu$ ($\varepsilon=1740$). Both the spectra indicate inflections at longer wavelengths and are nearly identical with that of thiostearic acid in shape.³⁾

In the infrared absorption spectrum of thiopalmitic acid measured by the potassium bromide-disk method (Fig. 3), an absorption band for the S–H group appears at 2545 cm^{-1} and an absorption band for the C=O group appears at 1665 cm^{-1}. On the other hand, in the infrared absorption spectrum of thiomyristic acid as measured by the liquid film method (Fig. 4), an absorption band for the S–H group appears at 2548 cm^{-1} and an absorption band for the C=O group appears at 1708 cm^{-1}. However, in the spectra of both acids, no absorption bands for the C=S group are observed. These facts indicate that the synthesized thiopalmitic and thiomyristic acids assume the thiolic acid form; this is in accordance with the view of Sheppared⁴⁾ and Crouch⁵⁾ that thioacetic acid has the thiolic acid form, and with the view of Hirabayashi et al.³⁾ that thiostearic acid also has the thiolic acid form.

As has been mentioned above, Auger et al. reported that thiopalmitic acid which was synthesized by the phenyl ester-sodium hydrogen sulfide method had the melting point of 71°C. As has previously been reported,⁶⁾ in this synthetic method a large quantity of diacyl disulfide is produced. Accordingly, judging from the melting point and synthetic method described by Auger et al., the substance which was reported to be thiopalmitic acid by Auger et al. is really dipalmitoyl disulfide or some substance in which dipalmitoyl disulfide is a principal component.*5 As a result of the present experiments, the melting point of thiopalmitic acid*6 should be corrected to 30.8—31.3°C, and the melting point of thiomyristic acid, which has been ambiguous, has been determined to be 19.8—20.3°C.

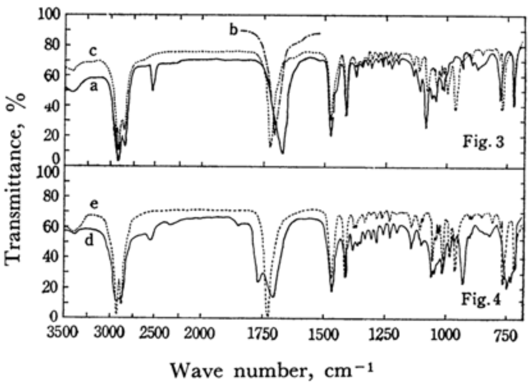

Fig. 3. Infrared absorption spectra.
a : Thiopalmitic acid (——) in KBr disk (1.50 mg./200 mg. KBr)
b : Thiopalmitic acid (—·—) in a chloroform solution
c : Dipalmitoyl disulfide (----) in KBr disk (1.30 mg./200 mg. KBr)

Fig. 4. Infrared absorption spectra.
d : Thiomyristic acid (——) in a liquid film
e : Dimyristoyl disulfide (----) in KBr disk (1.40 mg./200 mg. KBr)

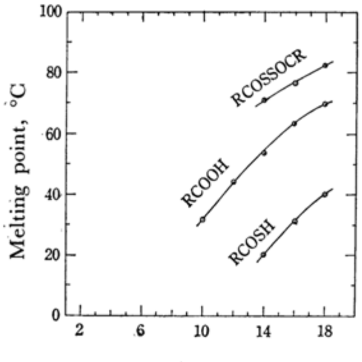

Fig. 2. Relations between number of carbon atoms and melting points of RCOSH and RCOSSOCR.

The relations between the number of carbon atoms and the melting point of higher aliphatic thio acids and diacyl disulfides are shown in Fig. 2.

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*3 The ultraviolet absorption spectra were measured by using a Shimadzu Quartz spectrophotometer, model QB-50, and silica cells (1 cm.).

4) N. Sheppard, *Trans. Faraday Soc.*, **45**, 693 (1949).

5) W. W. Crouch, *J. Am. Chem. Soc.*, **74**, 2926 (1952).

*4 Since the calculated amounts of each element in thiopalmitic acid and dipalmitoyl disulfide are nearly equal to each other, it is very difficult to distinguish and identify the one from the other by the results of elementary analysis. In the report of Auger et al., only the value of sulfur obtained by elementary analysis is described; the neutralization value for distinguishing them is not described. Moreover, it must be taken into consideration that it is possible to convert thiopalmitic acid into dipalmitoyl sulfide by the elimination of hydrogen sulfide during recrystallization or storage.

*5 E. g., in "Beilstein, Handbuch der Organischen Chemie," or E. E. Reid, "Organic Chemistry of Bivalent Sulfur IV," Chemical Publishing, New York (1962), p. 61, etc., the melting point of thiopalmitic acid has been given as 71°C, as given by Auger et al.

6) Y. Hirabayashi, M. Mizuta and T. Mazume, This Bulletin, **38**, 320 (1965).

Experimental

The Synthesis of Palmitoyl Chloride and Myristoyl Chloride.—The synthetic method used here was essentially identical with that described earlier for stearoyl chloride.[3]

Palmitoyl chloride (100 g.), with a b. p. of 148—149°C/2 mmHg, was synthesized in a 93.0% yield by the reaction of palmitic acid (100 g.; m. p. 61.5—62.0°C; neutralization value, 218.2) with freshly-distilled thionyl chloride (100 g.).

Myristoyl chloride (86 g.), with a b. p. of 145—148°C/5 mmHg, was synthesized in a 93.5% yield by the reaction of myristic acid (85 g.; m. p. 53.5—54.0°C; neutralization value, 245.9) with freshly-distilled thionyl chloride (85 g.).

The Preparation of a Sodium Hydrogen Sulfide-Ethanol Solution.—This was carried out according to the method described in a previous paper.[3]

The Synthesis of Thiopalmitic Acid.—The palmitoyl chloride (85 g.) was added, drop by drop and over a period of several minutes, to the above sodium hydrogen sulfide - ethanol solution (prepared from 20.0 g. of metallic sodium, 300 ml. of absolute ethanol, and hydrogen sulfide) while the solution was being vigorously stirred and heated at 65—70°C (molar ratio; $C_{15}H_{31}COCl : NaSH = 1 : 2.8$). Then the mixture was refluxed on a water bath for 1 hr., after which the ethanol was separated under a vacuum in the current of hydrogen to give a white jelly residue. The residue was dissolved in 1 l. of water, acidified with dilute hydrochloric acid, and extracted with ether. The ether layer was washed with water in order to remove the excess hydrochloric acid. An insoluble white matter suspended between the ether and the water was filtered off (0.8 g. (A)). The ether layer was dried over anhydrous sodium sulfate, and a crude product (78.0 g.) (B) was obtained by distilling off the ether (light yellow colored; m. p. 28—29°C (partly 45°C); neutralization value, 180.4; and sulfur content, 10.2 (by the iodine method) or 10.8% (by Kitamura's method)). By the fractional crsytallization of the product B (77.0 g.) from benzene, thiopalmitic acid (43.9 g., m. p. 30.8—31.3°C) was obtained as colorless crystals.

Found: neutralization value, 205.8; C, 70.26; H, 11.95; S, 11.64 (the iodine method), 11.80 (Kitamura's method).

Calcd. for $C_{16}H_{32}OS$: neutralization value, 205.9; C, 70.52; H, 11.84; S, 11.77%.

From the higher-melting point fraction and the product A, dipalmitoyl disulfide (3.4 g.) was obtained as colorless crystals (from benzene); m. p. 76.0—76.5°C, undepressed on admixture with an authentic specimen. (Found: S, 11.80. Calcd. for $C_{32}H_{62}O_2S_2$: S, 11.81 %. UV, Fig. 1; IR, Fig. 3).

From the lower-melting point fraction, ethyl palmitate was isolated.

As a result of the fractional crystallization, the compositions of the products (A and B) were found to be as follows: thiopalmitic acid 82.5%, dipalmitoyl disulfide 5.0%, and ethyl palmitate 12.5%.

The Synthesis of Thiomyristic Acid.—The myristoyl chloride (86.0 g.) was added, drop by drop and over about a 10-min. period, to the above sodium hydrgoen sulfide - ethanol solution (prepared from 32.0 g. of metallic sodium, 320 ml. of absolute ethanol, and hydrogen sulfide) while it was being vigorously stirred and heated at 70—75°C (molar ratio; $C_{13}H_{27}\cdot COCl : NaSH = 1 : 3.7$). Then, the mixture was refluxed on a water bath for 1 hr., after which the ethanol was separated under a vacuum in the current of hydrogen to give a white jelly residue. Water (1.5 l.) was added to the residue, and the ether-soluble matter (neutral fraction) therein was extracted several times with ether. Concurrently, the aqueous layer was acidified with dilute hydrochloric acid and extracted with ether (acidic fraction). Each ether layer was washed with water and dried over anhydrous sodium sulfate. When the ether was distilled off, there remained the neutral fraction (6.5 g.; m. p., below 25°C; neutralization value, 42.6; S, 2.4 (by the iodine method) or 2.5% (by Kitamura's method)) and the acidic fraction (78.0 g.; m. p., below 25°C; neutralization value, 221.9; S, 12.1 (by the iodine method) or 12.4% (by Kitamura's method)). By the fractional crystallization of the acidic fraction (70.0 g.) from hexane, thiomyristic acid (48.5 g.; m. p. 19.8—20.3°C) was obtained as colorless crystals.

Found: neutralization value, 228.8; C, 68.51; H, 11.70; S, 12.94 (the iodine method); 13.10 (Kitamura's method). Calcd. for $C_{14}H_{28}OS$: neutralization value, 229.5; C, 68.79; H, 11.55; S, 13.12%.

From the lower-melting point fraction, ethyl myristate was isolated, while from the higher-melting point fraction dimyristoyl disulfide (2.2 g.) was obtained as colorless crystals (from hexane), m. p. 70.5—71.5°C; undepressed on admixture with an authentic specimen. (Found: S, 13.20. Calcd. for $C_{28}H_{54}O_2S_2$: S, 13.17 %. UV, Fig. 1; IR, Fig. 4).

As a result of the fractional crystallization, the compositions of the acidic part were found to be as follows: thiomyristic acid 87.5%, dimyristoyl disulfide 3.5%, and ethyl myristate 9.0%.

On the other hand, the neutral fraction was confirmed by further recrystallization to consist of ethyl myristate (81.6%) and thiomyristic acid (18.4%).

The Synthesis of Dipalmitoyl Disulfide and Dimyristoyl Disulfide.—An iodine solution (ca. 1 N) was added, drop by drop, to a solution of thiopalmitic acid (3.0 g.) or thiomyristic acid (3.0 g.) in ether (20 ml.)-ethanol (20 ml.) until coloring was observed; the reaction mixture was then kept at room temperature for 1 hr.. The deposit was filtered off and thoroughly washed with ethanol to give a crude product.

The crude product from thiopalmitic acid was recrystallized repeatedly from benzene to give colorless, flaky crystals (2.5 g.) with a m. p. of 76.0—76.5°C.

Found: C, 70.59; H, 11.66; S, 11.80 (Kitamura's method). Calcd. for $C_{32}H_{62}O_2S_2$: C, 70.79; H, 11.51; S, 11.81%. UV (cf. Fig. 1): $\lambda_{max}^{cyclohexane}$, 224 m$\mu$ (ε=4260).

The crude product from thiomyristic acid was recrystallized repeatedly from hexane to give colorless, flaky crystals (2.5 g.) with a m. p. of 70.5—71.5°C.

Found: C, 68.83; H, 11.38; S, 13.20 (Kitamura's method). Calcd. for $C_{28}H_{54}O_2S_2$: C. 69.08; H, 11.18; S, 13.17%. UV (cf. Fig. 1): $\lambda_{max}^{cyclohexane}$, 223 m$\mu$ (ε=4260).

Infrared Absorption Spectra.—The infrared absorption spectra of thiopalmitic acid, dipalmitoyl disulfide, thiomyristic acid, and dimyristoyl disulfide are shown in Figs. 3 and 4. A Hilger H-800 infrared spectrophotometer was used for the measuring.

Thiopalmitic Acid.—In the spectrum measured by the potassium bromide-disk method, the S–H stretching band appeared at 2545 cm^{-1} and the C=O stretching band appeared at 1665 cm^{-1}. An absorption band, probably due to the S–H group, appeared at around 862 cm^{-1}. In the spectrum measured by the Nujol-mull method,[*6] the S–H stretching band was not evident; however, the C=O stretching band shifted to 1714 cm^{-1}. In the spectrum measured in a chloroform solution, the C=O stretching band shifted to 1707 cm^{-1}.

Thiomyristic Acid.—In the spectrum measured by the liquid film method, the S–H stretching band appeared at 2548 cm^{-1} and the C=O stretching band appeared at 1708 cm^{-1}. Since the thiomyristic acid used in the measuring was retained in the liquid state in a vacuum desiccator for a considerable period after the isolation from the reaction product, a part of the converted product, dimyristoyl sulfide, was contained in the sample.[*7] Accordingly, absorption bands appeared at 1763 and 926 cm^{-1} which did not appear in the spectra of such homologues as thiostearic or thiopalmitic acid; the two bands corresponded to the high-intensity absorption bands at 1766 and 932 cm^{-1} which appeared in the spectrum of distearoyl sulfide ($C_{17}H_{35}COSOCC_{17}H_{35}$).[7]

Dipalmitoyl Disulfide and Dimyristoyl Disulfide.—In the spectra measured by the potassium bromide-disk method, the C=O stretching bands appeared at 1712 in dipalmitoyl disulfide and at 1715 cm^{-1} in dimyristoyl disulfide.

[*6] A part of the sample is melted or dissolved in Nujol in the preparation of paste because of its low melting point.

[*7] When thiomyristic acid was retained in a vacuum desiccator in the liquid state, it was converted into dimyristoyl sulfide by the elimination of hydrogen sulfide. This will be reported on later in detail.

7) Y. Hirabayashi, M. Mizuta and T. Mazume, This Bulletin, **38**, 1099 (1965).