separated, dried with solid sodium hydroxide and fractionated. The fraction that boiled at 160–175° amounted to 29–31 g. On redistillation practically all of this fraction boiled at 168–172°. The yield of the dibromopyridine was 30–36% of the theoretical and that of the 3-bromopyridine 36–38% of the theoretical based on the bromine used in the preparation of the perbromide.

The separation of 3,5-dibromopyridine from 3-bromopyridine by steam distillation of the former from acid solution was originally used by Ciamician and Silber[3] and is fairly satisfactory but not complete. There appears to be some of the di-substitution product left with the monobromopyridine even after prolonged steam distillation, and in the final distillation of the latter compound a small amount of the dibromopyridine usually crystallizes in the condenser.

When the perbromide of higher bromine content was heated under similar conditions, a 40% yield of the dibromopyridine was obtained but none of the 3-bromopyridine was found. It was thought that dilution of this higher perbromide with pyridine hydrobromide might increase the yield of the mono-substituted product but several runs in which 2 moles of pyridine hydrobromide was mixed with 1 mole of the higher perbromide gave an average of 10% yield of 3-bromopyridine and 30% yield of the 3,5-dibromopyridine.

Summary

A convenient method of brominating pyridine to 3-bromopyridine and 3,5-dibromopyridine has been described. It consists of the preparation of a perbromide of pyridine hydrobromide in glacial acetic acid solution and the transformation of this perbromide by heat into the bromopyridines.

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SYNTHETIC GLYCERIDES. I. PREPARATION AND MELTING POINTS OF GLYCERIDES OF KNOWN CONSTITUTION[1]

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RECEIVED OCTOBER 22, 1928 PUBLISHED MARCH 6, 1929

The isolation of pure triglycerides from natural fats and oils is an uncertain and laborious process because of the difficulty of complete separation. Even when pure triglycerides have apparently been obtained satisfactory evidence is not available to indicate which of the possible isomers has been found. It was thought that progress could best be made through the synthesis of glycerides of known constitution and the study of their chemical and physical properties. Data thus obtained will be valuable in the study of the components of naturally occurring fats and oils.

It seemed probable that definite relationships might be found between certain physical properties of the fats and their molecular structure if sufficient data were available to warrant conclusions. The three sets of isomers (only one having fatty acids) prepared by Fischer[2] indicated that

[1] This paper is based upon a part of the theses submitted by H. P. Averill and J. N. Roche to the Graduate School, University of Pittsburgh, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] E. Fischer, *Ber.*, **53**, 1621 (1920).

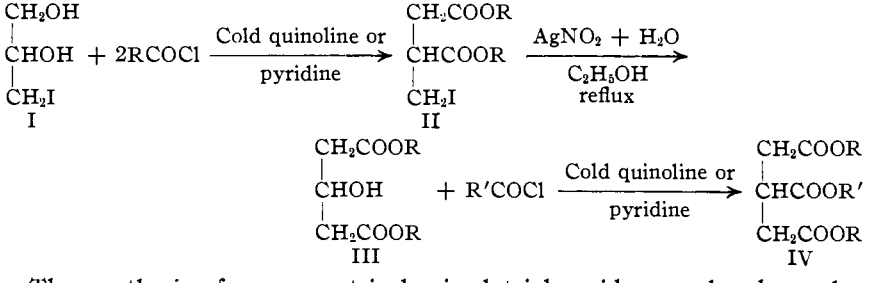
the unsymmetrical glycerides melt at a lower temperature than their symmetrical isomers and may differ somewhat in solubility, but much of the data in the literature is in conflict with this generalization.

A review of the literature on the synthesis of fats shows that there are seven general methods for preparing simple and mixed glycerides.[3] Only two or possibly three of these methods, however, are found to be of value in the preparation of glycerides in which the position of the acyl groups can be stated with certainty. Four of the general methods are due to Grün and his co-workers and much of the data on synthetic glycerides found in the literature is based on these reactions. Three of Grüns' methods have been found to result in an unpredictable rearrangement of the acyl groups. It is found that the replacement of an OH group in glycerol at elevated temperatures by an acyl chloride or the replacement of a halogen by an OH group will always allow of a shifting of the acyl groups already present into their most natural positions. Not only is the separation of the individual components of such mixtures difficult to perform but they are further complicated because at the temperatures employed there can be reactions between two moles of the partly acylated glycerides.

The preparation of glycerides from halohydrins and soaps, a fourth method used extensively by Grün, while allowing of greater freedom from shifting, permits of side reactions of considerable magnitude.

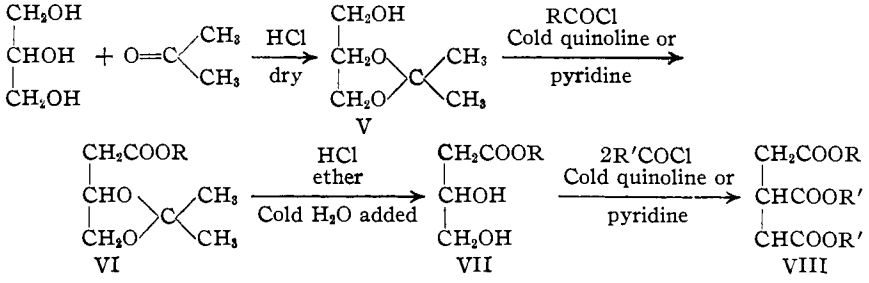
Fischer, shortly before his death in 1920, devised an entirely new method for the preparation of unsymmetrical triglycerides and greatly improved the synthesis of symmetrical di- and triglycerides and by these methods glycerides can now be prepared whose chemical structure is reasonably certain.

The synthesis of symmetrical mixed glycerides by the Fischer method can best be shown by the following reactions



The synthesis of unsymmetrical mixed triglycerides can be shown by the following reactions

[3] A. Grün and E. Theimer, *Ber.*, **40**, 1792 (1907); A. Grün and P. Schacht, *ibid.*, **40**, 1778 (1908); A. Grün and F. Wittka, *ibid.*, **54B**, 273, 290 (1921); A. Fairbourne and G. E. Foster, *J. Chem. Soc.*, **127**, 2760 (1925); E. Abderhalden and E. Eichwald, *Ber.*, **48**, 1849 (1915); E. Fischer, M. Bergwin and H. Barwind, *ibid.*, [2] **53**, 1589 (1920); C. Amberger and K. Bromig, *Biochem. Z.*, **130**, 252 (1922).



No temperatures higher than 30–35° need be employed in these syntheses except for the conversion of the diacylated iodohydrin wherein the alcohol mixture is refluxed and the acyl group shifts from the β- to the α-position following hydrolysis of the halide. All intermediate compounds can be purified by crystallization or vacuum distillation before use in the next step.

Thus it is only within the last few years that a study of the physical properties of the isomeric glycerides has been possible. In view of the uncertainty of the data for many of the mono-, di- and triglycerides reported in the literature, this investigation was undertaken (a) to recheck many of the values given in the literature, (b) to synthesize other glycerides by methods which have been found satisfactory and (c) to find what relation exists between the constitution of the isomeric glycerides and their physical properties. Data are included in this paper only with respect to their melting points. Further data will be given in later papers.

Preparation of Acyl Chlorides.—Acyl chlorides were prepared by the use of oxalyl chloride and fatty acid according to the directions given by Adams and Ulich.[4] The following acyl chlorides were prepared: *n*-capryl, b. p. 104–105 (9 mm.); myristyl, b. p. 134° (2.5 mm.); stearyl, b. p. 165° (0.4 mm.); lauryl, b. p. 150° (22 mm.); caproyl, b. p. 138–140° (atmos.).

Stearyl chloride could only be distilled when the distilling flask was immersed up to the side arm in a special oil-bath. The top of the bath was heated by means of a hot-plate and the temperature maintained throughout the bath at 167°. All compounds of this type were kept in desiccators over phosphorus pentoxide.

Preparation of α-Monoglycerides.—The preparation of α-monomyristin will show the general procedure used in the preparation of monoglycerides.

To a mixture of 8.82 g. (1.1 moles) of acetoneglycerin and 8.85 g. (1.1 moles) of quinoline (pyridine used for low mol. wt. fatty acids) contained in a thin, glass-stoppered iodine flask, there was added, with cooling in an ice-bath, 15 g. (1 mole) of myristyl chloride. After standing at room temperature for two days, it was treated with 100 cc. of ether and 60 cc. of ice-cold, 0.5 *N* sulfuric acid. The mixture was shaken in a separatory funnel and the acid layer drawn off. After several washings with the ice-cold acid, no test for quinoline was found and the ether layer was then thoroughly

[4] R. Adams and L. Ulich, THIS JOURNAL, **42**, 599 (1920).

shaken several times with 75-cc. portions of potassium bicarbonate and finally washed well with water. After drying over fused sodium sulfate, the ether was evaporated and the myristylacetoneglycerin purified.

The hydrolysis of the acetone compound was carried out by two different methods. (a) To the acetone compound obtained above dissolved in 75 cc. of ether, 80 cc. of concentrated hydrochloric acid was slowly added. The mixture was kept in a cold water-bath for half an hour and then treated with 300 cc. of water. The mixture was next placed in a freezing mixture and the monomyristin soon separated in the form of fine white crystals. After suction-filtering and washing with water, the crystals were dried over phosphorus pentoxide and crystallized from a 1:1 mixture of ether and petroleum ether. Lustrous plates or leaves separated which melted at 67.3°; the melting point did not change on repeated recrystallization.

(b) Ten grams of the myristylacetoneglycerin was shaken with 40 cc. of 0.25 *N* sulfuric acid at 45°. The mixture was left in a 40°-oven for twenty-four hours. It was then cooled to 0° and treated with a slight excess of barium hydroxide. The excess hydroxide was removed by carbon dioxide and the mixture evaporated without filtration at 40°. The residue was treated with chloroform and the chloroform solution filtered from the carbonate and sulfate and dried over fused sodium sulfate. After evaporation of the chloroform the monomyristin was crystallized from 1:1 ether and petroleum ether; melting point 67.2°.

The following α-monoglycerides were prepared according to the above method.

Compound	M. p., °C., found	Previously recorded
α-Monopalmitin	77.0	78–79 (a), 77.6 (d), 63 (h), 72 (g), 65 (e), 58(i)
α-Monomyristin	67.3	68 (g), 68 (j)
α-Monocaprin	51.4	
α-Monolaurin	63.0	62–63 (a), 52 (b), 61 (c), 59 (b), 58 (c)
α-Monostearin	81.1	81–82 (a), 80.9 (d), 73 (e), 61 (f), 78 (g)
α-Monoacetin	Not distilled	

(a) *Ber.*, **53,** 1589 (1920); (b) *ibid.*, **42,** 3750 (1909); (c) *ibid.*, **43,** 1283 (1910); (d) *Biochem. Z.*, **130,** 252 (1922); (e) *Z. Biol.*, **44,** 78 (1903); (f) *Chim. Org. Syn.*, II, 65 (1860); (g) *Ber.*, **36,** 4339 (1903); (h) *Ann.*, **6,** 225 (1884); (i) *Chim. Org. Syn.*, II, 75 (1860); (j) *Ber.*, **45,** 3420 (1912).

Preparation of α,α-Diglycerides.—α,α-Diglycerides were prepared according to the following method, showing the preparation of α, α-dilaurin.

Ten and one-tenth g. (1 mole) of α-iodohydrin in 13.8 cc. (1 mole) of quinoline was cooled to 0° in ice water. To the mixture, which was kept cold, 22.0 g. (1 mole) of lauryl chloride in 42 cc. of chloroform was added in several portions. After standing at room temperature for forty-eight hours the red-colored reaction mixture was taken up with 400 cc. of ether and 100 cc. of ice-cold 0.5 *N* sulfuric acid. The washing with acid, bicarbonate and water was carried on in the same manner as for monoglycerides. After drying the solution the ether was evaporated and the α-iodo-dilaurin remained as a colorless oil. By dissolving in a mixture of ether and methyl alcohol (1:3) and cooling to −15° the iodine compound was obtained as white crystals melting at 23.5°.

Twenty-four grams of α-iodo-α,β-dilaurin was refluxed on a water-bath in a mixture of 150 cc. of ethyl alcohol, 21 cc. of water and 24 g. of silver nitrite for one hour. After the separation of silver iodide, the reaction mixture was filtered hot. The filtrate was evaporated on a water-bath and left behind an oil mixed with silver compounds. The oil was taken up with 100 cc. of absolute alcohol, filtered and again evaporated. This time it was boneblacked to clear it. By slow evaporation of the alcohol the α,α-dilaurin crystallized in shining plates. After drying over phosphorus pentoxide in a vacuum

desiccator the α,α-dilaurin melted sharply at 56.6°. Repeated crystallization did not change the melting point. The mother liquor crystals of the second recrystallization melted at 56.4–56.6°.

The following α,α-diglycerides were prepared in the above manner.

Compound	M. p., °C., found	Previously recorded
α,α-Dilaurin	56.6	55 (d), 57 (c), liquid (e)
α,α-Distearin	79.1	78.2 (c), 76.5 (f), 74.5 (g), 76 (a), 78.5–9 (h)
α,α-Dipalmitin	69.5	70 (a), 69 (b), 69.5 (i)
α,α-Dimyristin	63.8–64.4	61 (c), 63 (d)

(a) *Ber.*, **38**, 2285 (1905); (b) *Z. Biol.*, **44**, 88 (1913); (c) *Ber.*, **40**, 1797 (1907); (d) *ibid.*, **40**, 1785 (1907); (e) *Ber.*, **45**, 3691 (1912); (f) *J. prakt. Chem.*, **28**, 227 (1883); (g) *Z. Biol.*, **44**, 78 (1903); (h) *Ber.*, **53**, 1621 (1920); (i) *Biochem. Z.*, **130**, 252 (1922).

Synthesis of Triglycerides.—For the preparation of symmetrical mixed triglycerides the preparation of β-stearo-α,α-dilaurin is used as an example.

Four grams of α,α-dilaurin (1 mole) was dissolved in 5 cc. of chloroform and 1.42 g. (1.2 moles) of quinoline added. The flask containing this mixture was then placed in ice water and 2.9 g. (1.1 moles) of stearyl chloride in 2 cc. of chloroform was slowly added. After standing at room temperature for forty-eight hours, it was taken up with 300 cc. of ether and 100 cc. of ice-cold 0.5 *N* sulfuric acid and treated in the above manner for the separation of quinoline. After drying the solution over fused sodium sulfate, the ether was evaporated slowly, mostly at room temperature. The addition of alcohol to the chloroform remaining after evaporation of the ether caused a separation of the triglyceride. After drying over phosphorus pentoxide the glyceride melted at 49.8°. After two recrystallizations the melting point rose to 50.9° and was not changed by further crystallization.

For unsymmetrical mixed triglycerides, the monoglycerides were treated with two moles of an acyl halide and quinoline. The following triglycerides were prepared. Melting points and saponification numbers were taken as the best index of purity.

Compound	M. p., °C., found	Previously recorded
Trilaurin	45.6	45 (a), 45 (b), 46.4 (b)
β-Stearo-α,α-dilaurin	50.9	37.5 (e)
α-Stearo-α,β-dilaurin	45.4	46.0 (d)
β-Lauro-α,α-dimyristin	49.2–49.5	46.5 (e)
α-Lauro-α,β-dimyristin	48.5	45 (d)
β-Palmito-α,α-dimyristin	59.8–60.0	
α-Palmito-α,β-dimyristin	53.0	
β-Stearo-α,α-dipalmitin	64.8	59.1 (f), 63.3 (g), 60 (b)
α-Stearo-α,β-dipalmitin	62.6	63.5 (f), 60 (b)
β-Aceto-α,α-dipalmitin	54.0	49 (i)
α-Aceto-α,β-dipalmitin	51–52	67 (i)
β-Capro-α,α-dipalmitin	66.0	
α-Capro-α,β-dipalmitin	60.0	
β-Lauro-α,α-dipalmitin	63.5–64	
α-Lauro-α,β-dipalmitin	54.5	
β-Myristo-α,α-dipalmitin	58.5–59	
α-Myristo-α,β-dipalmitin	55.5	
β-Aceto-α,α-distearin	62.7	64.0 (c), 56.5 (e)

Compound	M. p., °C., found	Previously recorded
α-Aceto-α,β-distearin	56.6	59 (c), 44 (d)
α-Lauryl-α,β-distearin	50.9	49.5 (h), 49 (d)

(a) *Ber.*, **45**, 3691 (1912); (b) Lewkowitsch, **1921**, Vol. I, 6th ed., p. 26; (c) *Ber.*, **53**, 1621 (1920); (d) *ibid.*, **40**, 1792 (1907); (e) *ibid.*, **40**, 1780 (1907); (f) *Biochem. Z.*, **130**, 252 (1922); (g) *J. Chem. Soc.*, **129**, 1458 (1926); (h) *Ber.*, **53**, 1589 (1920); (i) *ibid.*, **38**, 2284 (1905).

Discussion of Results

It is evident from the above data that there was a considerable difference in the melting points of many of the compounds previously prepared and those described in this work.

In the case of the previously recorded isomeric stearodipalmitins mixtures of the mono- or dipalmitins and fatty acid were heated. The positions of acyl groups in a mixed glyceride cannot be stated with certainty when using this procedure. Both recorded compounds showed melting points of 60° when prepared by this method. The use of high temperatures also accounts for the faulty results recorded for the acetodipalmitins and the acetodistearins. The reaction between acetic anhydride and α,α-diglycerides can be accomplished in the cold if pyridine is added.

Symmetrical stearodilaurin as prepared by Grün melts 13° below the compound reported here. He prepared it by the same method used here except that in his method no quinoline was used for the removal of hydrogen chloride and the mixture was heated. This type of reaction is incomplete and extensive shifting of the acyl groups takes place, giving a mixture of triglycerides. The same criticism holds for his symmetrical laurodimyristin, which he prepared by the same method and found to be mixed with other unidentified substances.

Many of the unsymmetrical triglycerides previously recorded in the literature, prepared from diacylchlorohydrins and soaps, are in good agreement with those reported here. It is to be noted, however, that the replacement of the chlorine does not take place smoothly and considerable amounts of by-products form, giving low yields. The following compounds prepared by this method agree with those prepared during the present investigation: α-laurodistearin, α,α-dilaurin, α-stearodilaurin, β-stearodipalmitin, α-monostearin, and trilaurin.

The simple triglycerides, trilaurin and trimyristin, both of which were prepared from the α,α-diglycerides using acyl chloride and quinoline, agree very well with the melting points of the same compounds recorded in the literature and prepared by other methods.

In several cases the mono- and diglycerides which were used in preparing the triglycerides recorded in the literature were from 3 to 5° lower in melting point than those herein reported.

In the nine sets of isomeric glycerides reported here the symmetrical isomer in each case was found to have the higher melting point. This was

not the case in three of the five sets of isomers for which values could be found in the literature (acetodipalmitins, stearodilaurins and stearodipalmitins). The average difference in melting points between the symmetrical and unsymmetrical isomers for the nine sets prepared is 4.7°.

Fischer's methods have been used for the first time in the preparation of α-monocaprin, α-monomyristin, α,α-dilaurin, α,α-dimyristin and for the following sets of isomers: the stearodilaurins, acetodipalmitins, caprodipalmitins, laurodipalmitins, myristodipalmitins and the laurodimyristins. The caprodipalmitins, laurodipalmitins and myristodipalmitins had not been prepared previously.

Summary

1. The methods devised by Emil Fischer for the synthesis of unsymmetrical and symmetrical mixed glycerides have been extended to the preparation of glycerides not previously synthesized and used to recheck many of the data reported in the literature.

2. In rechecking data available for eleven triglycerides, differences between the melting points of the compounds previously prepared and those described in this work have been found. The differences are shown to be due to the methods of preparation used and the reasons for these differences are indicated.

3. The following new triglycerides have been prepared: the isomeric caprodipalmitins, laurodipalmitins, myristodipalmitins and palmitodimyristins.

4. In the synthesis of triglycerides, the following new intermediate compounds have been prepared: caprylacetoneglycerin, α-monocaprin, α-iododilaurin, α-iododimyristin.

5. It was found that the symmetrical isomer in each of the nine sets of isomeric triglycerides made had a higher melting point than that of the unsymmetrical isomer.

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