[CONTRIBUTION NO. 565 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Synthetic Triacid Triglycerides of Saturated Fatty Acids[1,2,3]

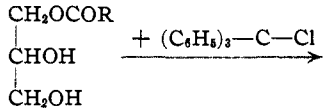
BY CHIADAO CHEN AND B. F. DAUBERT

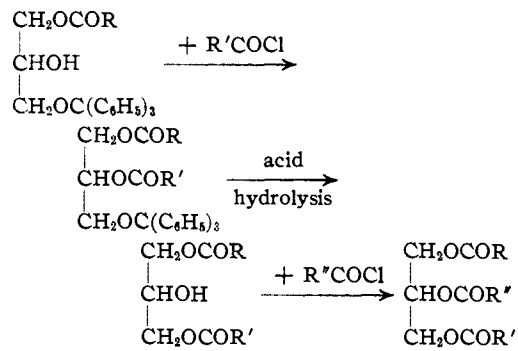
Much of the work in this Laboratory the past several years has involved the preparation and characterization of symmetrical and unsymmetrical diacid triglycerides of both saturated and unsaturated fatty acids. It is anticipated that the molecular structure interpretations of these compounds deduced from X-ray diffraction data and other physical properties will soon be published.

More recently our attention has been focused on the synthesis of triglycerides containing three different saturated fatty acids. Although the preparation of several triacid triglycerides was reported by Grün and Slepnik[4] in 1909, it was not until the investigations of Verkade, *et al.*,[5] that the methods of synthesis were placed on a reliable basis. Verkade made the observation that a 1-monoglyceride reacts with trityl chloride (triphenylmethyl chloride) to produce an easily separable 1-acyl-3-tritylglycerol with the 2-hydroxyl group unreacted. This fact makes possible the introduction of a second acyl group differing from the one present in the original monoglyceride. Acid hydrolysis of the trityl group from the 1,2-diacyl-3-tritylglycerol is accompanied by a migration of the acyl group in the 2-position to the 3-position which was formerly occupied by the trityl group. The resulting 1,3-diacid diglyceride may then be esterified in the 2-position by a third fatty acid.

An alternative method[6] for the preparation of a triacid triglyceride involves the removal of the trityl group from a 1,2-diacyl-3-tritylglycerol by hydrogenolysis in neutral solution. The shift of the acyl group from the 2- to the 3-position does not occur during this treatment and, as a consequence, the unsymmetrical diacid 1,2-diglyceride may then be esterified in the 3-position with a different fatty acid.

In the present investigation, advantage was taken of acyl migration from the 2- to the 3-position by acid hydrolysis during removal of the trityl group to prepare a series of triacid glycerides. The reactions starting with the 1-monoglycerides are





Molecular weights, refractive indices, melting points, and solubilities were used as criteria for identity and purity. Carbon and hydrogen percentages[7] for the determination of purity were of little value and only one such determination is reported to indicate that no gross errors were involved in the synthesis.

In agreement with previous studies in this Laboratory and by other investigators on the different crystal modifications of synthetic glycerides, evidence has been obtained from both capillary tube and thermometric measurements that the triacid triglycerides are polymorphic.

In conformity with the system of nomenclature used previously for the polymorphic forms as indicated from thermal curve data, Form I, II, etc., are again applied to this group of triacid triglycerides. Form I always refers to the highest melting form. The melting points of the different crystal modifications are listed in Table I.

Significant and somewhat surprising was the observation that crystallization of several of the triglycerides from solvent did not always result in the isolation of the crystals in their highest melting modification. Although it has been usual to accept the fact that solvent crystallized triglycerides are the most stable and the highest melting, other investigators[4,8] in a few instances have reported the isolation from solvent of the different melting modifications of the same triglycerides. Verkade,[8] in particular, noted that 1-stearyl-2-myristyl-3-palmitylglycerol crystallized from a 1:3 benzene–ethyl alcohol mixture melted at 59.5–60°. He also obtained, presumably from the same mixture of solvents, a labile modification melting at 55–56°. After our observations on other triacid triglycerides, we confirmed the melting point data obtained by Verkade on 1-stearyl-2-myristyl-3-palmitylglycerol, as indicated in Table I.

Our original observations on the crystallization

(1) For other papers in this series see THIS JOURNAL, **65**, 2142, 2144 (1943); **66**, 53, 289, 290, 690, 997, 1507 (1944).

(2) The authors are indebted to Swift and Company and the Buhl Foundation for grants in support of this investigation.

(3) "Triacid triglycerides" is used in this report to describe those triglycerides consisting of three different fatty acids. On this basis symmetrical and unsymmetrical triglycerides containing two different fatty acids may be referred to as "diacid triglycerides," and simple triglycerides as "monoacid triglycerides."

(4) Grün and von Slepnik, *Ber.*, **42**, 3740 (1909).

(5) Verkade and van der Lee, *Rec. trav. chim.*, **55**, 267 (1936).

(6) Verkade, *ibid.*, **62**, 393 (1943).

(7) Daubert, Fricke and Longenecker, THIS JOURNAL, **65**, 2142 (1943).

(8) Verkade, van der Lee and Meerburg, *Rec. trav. chim.*, **56**, 365 (1937).

TABLE I

		$n^{60.6}D$[a]	Mol. wt.[b] Calcd.	Found	M. p., °C. Form I	Form II	Form III
1-Stearyl-2-acyl-3-palmitylglycerol	myristyl[c]	1.44373	807	816	59.5	56.1	40.6
	lauryl	1.44286	779	787	57.5	56.0	32.0
	capryl	1.44226	751	746	55.0	53.8	20.1
1-Stearyl-2-acyl-3-myristylglycerol	palmityl[c]	1.44362	807	791	58.5	56.0	40.3
	lauryl[d]	1.44217	751	736	55.0	51.9	28.8
	capryl	1.44173	723	717	52.5	50.1	14.0
1-Stearyl-2-acyl-3-laurylglycerol	palmityl	1.44304	779	783	52.0	47.0	33.4
	myristyl	1.44196	751	744	49.5	45.5	27.5
	capryl	1.44068	705	691	41.8		22.3
1-Stearyl-2-acyl-3-caprylglycerol	palmityl	1.44219	751	764	50.0	46.5	26.1
	myristyl	1.44133	723	727	45.0	42.0	21.5
	lauryl	1.44048	705	704	44.0	40.0	14.5

[a] The average dn/dt for the triglycerides is 0.00039. Average differences in refractive index between isomeric pairs is 0.00019. [b] Molecular weights were determined by the method of Hanson and Bowman, *Ind. Eng. Chem., Anal. Ed.*, 11, 440 (1939). [c] Verkade, van der Lee and Meerburg[8] reported 59.5–60° and 58.5–59°, respectively, for these two compounds. [d] *Anal.* Calcd. for $C_{47}H_{90}O_6$: C, 75.14; H, 12.07; Found: C, 75.14; H, 11.98. The microchemical analysis was performed by the Microchemical Laboratory, California Institute of Technology, Pasadena, California. [e] Repeated attempts to crystallize this compound in a higher melting point modification were not successful. Since no other modification melting between 22.3 and 41.8° was found, Form I may well be a mixture of two different forms.

of at least two modifications from solvent were made during solubility measurements of the group of 1-stearyl-2-acyl-3-caprylglycerols in various solvents. For example, 1-stearyl-2-lauryl-3-caprylglycerol was crystallized normally from a mixture of ethyl and methyl alcohols during the course of its preparation and purification. The product melted at 39–40° as observed by the capillary tube method. During the solubility measurements of this triglyceride in acetone and in ether, our procedure involved the saturation of the solvent (ether or acetone) at a temperature approximating 30°. The saturated solution was then equilibrated for a period of twelve or more hours in a constant temperature water-bath maintained at 25 ± 0.01°. The crystalline product which separated melted at 43–44° after removal of the solvent, *in vacuo*, at room temperature. The difference of approximately 5° in melting point immediately suggested solvent of crystallization, but vacuum drying of the two crystalline products at temperatures slightly below their melting points did not change the final temperatures of melting. Crystallization of the form melting at 43–44° from ethyl ether or acetone by rapid cooling yielded the form melting at 39–40°. These observations seemed to suggest that crystallization of this triacid triglyceride from solvent under different conditions gave rise to the isolation of the product in two crystal modifications of different melting points.

Conclusive evidence for the two crystal modifications was obtained from X-ray diffraction data. The modification originally crystallized from the ethyl ether–methyl alcohol (m. p. 39–40°) exhibited an X-ray diffraction pattern typical of the β'-pattern[9] and the higher melting form (m. p. 43–44°) which was crystallized at 25° from acetone or ether showed the typical β-pattern. Complete X-ray diffraction data on the triacid triglycerides reported here will be the subject of a later publication.

(9) See E. S. Lutton, THIS JOURNAL, 67, 524 (1945).

With the exception of the 1-stearyl-2-capryl-3-laurylglycerol (m. p. 41.5–42°), the same phenomena were observed in the crystallization of other members of the series of 1-stearyl-2-acyl-3-laurylglycerols and the 1-stearyl-2-acyl-3-caprylglycerols.

It may be observed from the solubility data in Table II that the 1-stearyl-2-acyl-3-palmitylglycerols and the 1-stearyl-2-acyl-3-myristylglycerols are much less soluble in ethyl ether and petroleum ether than the 1-stearyl-2-acyl-3-laurylglycerols and the 1-stearyl-2-acyl-3-caprylglycerols. The solubility difference of these groups in each of the solvents is very pronounced and should be of considerable assistance in their separation and identification in mixtures. As was expected, the solubilities, in general, increased with decreasing carbon chain length of the saturated fatty acids.

TABLE II

SOLUBILITIES OF THE TRIACID TRIGLYCERIDES

		Grams of solute per 100 g. of solvent at 25 ± 0.01° Ethyl ether	Petroleum ether	Acetone	Ethyl alcohol
1-Stearyl-2-acyl-3-palmitylglycerol	myristyl	10.97	7.59	.18	.03
	lauryl	16.49	9.49	.31	.03
	capryl	22.87	10.60	.59	.03
1-Stearyl-2-acyl-3-myristylglycerol	palmityl	11.03	5.46	.18	.03
	lauryl	30.68	16.26	.68	.04
	capryl	53.75	37.03	1.96	.08
1-Stearyl-2-acyl-3-laurylglycerol	palmityl	72.63	58.88	1.47	.06
	myristyl	112.59	81.44	2.53	.07
	capryl	192.13	179.56	13.49	.39
1-Stearyl-2-acyl-3-caprylglycerol[a]	palmityl		89.97	2.38	.09
	myristyl		116.35	9.03	.31
	lauryl		148.42	26.04	.36

[a] It was difficult to obtain quantitative solubility data on this group of compounds in ethyl ether. The solutions possessed a tendency to gel during equilibration because of the great solubility of these compounds in this solvent.

The data in Table II also show the marked differences in the solubilities of the triacid triglycerides in the polar and non-polar solvents.

Experimental

Preparation of Intermediates.—All acid chlorides of saturated fatty acids of C_{10} to C_{18} carbon atoms inclusive were prepared from highly purified fatty acids[7] and thionyl chloride by the method of MacMasters and Ahmann.[10]

The 1-monostearin, m. p. 81–82°, from which all other intermediates were synthesized, was prepared according to the method of Malkin and Shurbagy.[11]

Preparation of 1-Stearyl-3-tritylglycerol.—This compound was prepared by the method of Verkade and van der Lee;[5] m. p. 66.0° (Verkade, 67°).

Preparation of 1-Stearyl-3-caprylglycerol.—1-Stearyl-3-tritylglycerol (42 g.) was dissolved in a mixture of pyridine (30 ml.) and benzene (42 ml.) and to this solution there was added slowly capryl chloride (20 g.). After shaking thoroughly, the mixture was refluxed on a steam-bath for two hours. The mixture, after it was cooled to room temperature, was dissolved in ethyl ether and the ether solution then washed successively with distilled water, 0.05 *N* sulfuric acid, 5% potassium bicarbonate solution, and distilled water, and finally dried over anhydrous sodium sulfate. After filtration and removal of the ether from the filtrate *in vacuo*, the liquid residue was dissolved in dry petroleum ether (192 ml.). The petroleum ether solution was cooled to approximately 5° in an ice-bath. Dry hydrogen chloride was passed into the solution for twenty minutes. After allowing the mixture to stand several hours at room temperature, it was taken up in ethyl ether (300 ml.). The solution was washed successively with distilled water, 5% potassium carbonate solution, again with distilled water, and then dried over anhydrous sodium sulfate. After several crystallizations at 5° from ether, the vacuum-dried product melted at 58.5–59.5°; molecular weight, 507 (calcd. 513); yield, 24.1 g. (67.2%).

1-Stearyl-3-palmitylglycerol, m. p. 70–71° (Verkade,[5] 71–71.5°), 1-stearyl-3-myristylglycerol, m. p. 64.5–65.5° (Verkade,[5] 66–66.5°), and 1-stearyl-3-laurylglycerol, m. p. 60.6–61.5° (Daubert,[12] 62°), were prepared in a similar manner.

Preparation of 1-Stearyl-2-lauryl-3-caprylglycerol.—1-Stearyl-3-caprylglycerol (7 g.) was dissolved in a mixture of palmityl chloride (3.5 g.) and pyridine (7 ml.) and then refluxed on a steam-bath for two hours. The reaction products after cooling to room temperature were treated with ethyl ether (600 ml.). The ether solution was washed and dried as described for 1-stearyl-3-caprylglycerol. After removal of the ether from the filtered solution, *in vacuo*, the triglyceride was crystallized from a mixture of ethyl ether (20 ml.) and methyl alcohol (50 ml.). Recrystallization several times from the same mixture of solvents and finally from acetone yielded a product melting at 39–40°; yield, 6.75 g. (70.1%); molecular weight, 704 (calcd. 705); $n^{60.0}D$ 1.44048.

Constants for other triacid triglycerides prepared in a similar manner are listed in Table I.

Polymorphism of the Triacid Triglycerides.—The thermometric techniques which were used to determine the transition temperatures of the different polymorphic forms have been described in previous publications[13,14].

Solubility Determinations.—The solubilities of the triacid triglycerides were determined at 25 ± 0.01° in ethyl alcohol, acetone, petroleum ether (b. p. 35–50°), and ethyl ether. Each solvent was carefully purified and dried by an accepted method of purification.

As previously stated, each solvent was saturated with solute at a temperature of approximately 30°. The solution was then equilibrated in a constant temperature bath for a period of twelve or more hours. The solute from a weighed portion of saturated solution was dried to constant weight *in vacuo*.

Summary

Physical data are reported for several series of synthetic triacid triglycerides.

(10) MacMasters and Ahmann, THIS JOURNAL, **50**, 147 (1928).

(11) Malkin and Shurbagy, *J. Chem. Soc.*, 1628 (1936).

(12) Daubert and Longenecker, *ibid.*, **66**, 53 (1944).

(13) Daubert and Clarke, *ibid.*, **66**, 690 (1944).

(14) Daubert and Clarke, *Oil and Soap*, **22**, 113 (1945).

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Chemical Reactivity of Myosmine

BY PAUL G. HAINES, ABNER EISNER AND C. F. WOODWARD

It was previously reported that myosmine (I), 2-(3-pyridyl)-Δ^2-pyrroline, had been produced in fair yields by the pyrolysis of nicotine.[2] Since prior work on myosmine was limited to reactions selected to establish the structure of the alkaloid,[3,4] a more extensive investigation of its chemical reactivity has been undertaken in the present study. Particular attention has been directed to reduction products and to derivatives of 3-pyridyl-ω-aminopropyl ketone (II), the open chain hydrolytic product of myosmine.

Data previously reported on the hydrolysis of Δ^2-pyrrolines by water appear to be in disagreement. The reaction of 2-methyl-Δ^2-pyrroline with hydroxylamine, semicarbazide and phenylhydrazine in aqueous solution led Marz to conclude that an equilibrium existed between the cyclic form and the open chain primary amino ketone.[5] However, the several 1-methyl-2-alkyl-Δ^2-pyrrolines prepared and studied by Craig[6] apparently were not hydrolyzed by water, since no reaction took place with phenylhydrazine or semicarbazide. Basicity data obtained by Adams and Mahan[7] on a number of 1,2-dialkyl-Δ^2-pyrrolines supported the assumption "that only a single molecule" was involved in the titrations.

N-Alkyl-Δ^2-pyrrolines are generally not hydrolyzed in aqueous solution, whereas the corre-

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Woodward, Eisner and Haines, THIS JOURNAL, **66**, 911 (1944).

(3) Späth, Wenusch and Zajic, *Ber.*, **69**, 393 (1936).

(4) Späth and Mamoli, *ibid.*, **69**, 757 (1936).

(5) Marz, Diss., Techn. Hochsch., München, 1913.

(6) Craig, THIS JOURNAL, **55**, 295 (1933).

(7) Adams and Mahan, *ibid.*, **64**, 2588 (1942).