ADVANCES IN THE SYNTHESIS OF GLYCERIDES OF FATTY ACIDS

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CONTENTS

I. INTRODUCTION

The chemistry of synthetic glycerides of fatty acids was reviewed by Daubert and King (40) in 1941. The present review describes recent progress in this field and covers the period from 1940 to December, 1957. Its purpose is to outline methods of glyceride synthesis developed during this period, to supply the characteristics of the synthesized products, and to outline some recent techniques used in the estimation and definition of glycerides. The discussion will be limited to glycerides of fatty acids with the exclusion of the related phospholipides. The synthesis of optically active glycerides, however, will be reviewed, since these glycerides seem to form an integral part of fats.

Accounts of synthetic glycerides may be found in textbooks such as that of Hilditch (73) or Ralston (126) and from time to time in the section on lipides of the *Annual Reviews of Biochemistry*, but no review as comprehensive as that of Daubert and King (40), previously mentioned, seems to have appeared in recent years. The excellent survey by Verkade (144) of the synthesis of glycerides deals essentially with the work carried out in his laboratory.

After the manuscript of this article had been completed an article by Malkin and Bevan (102) on the synthesis of glycerides appeared.

[1] Trityl = triphenylmethyl.

II. GENERAL CONSIDERATIONS

The nomenclature of glycerides, which lacks consistency, requires a brief reference. There is no agreement as to the designation of the carbon atoms of glycerol, both Greek letters and numbers being used. In conformity with the previous review in this Journal the symbols α, β, and α' have been retained. To avoid confusion the various crystalline forms of glycerides, which are at present the subject of much controversy, will be denoted with Roman numerals. The terms "simple" diglycerides and triglycerides and the slightly ambiguous terms "diacid" diglycerides (diglycerides with two different acyl groups) and "diacid" and "triacid" triglycerides (triglycerides with two similar and three different acyl groups, respectively) will be used throughout the text for the sake of brevity. Strictly speaking, even the terms monoglyceride, diglyceride, and triglyceride are misnomers; nevertheless they are generally accepted in the chemical nomenclature.

The danger of acyl migration and intermolecular exchange of fatty acids in the course of synthesis is now generally recognized, and this knowledge has eliminated the source of many previous errors. On the other hand, the purification of starting materials is not always effected with sufficient care, and results of some interesting recent investigations have been impaired because of the insufficient purity of the fatty acids used. Despite the extensive literature on the subject the synthesis of glycerides is still an art which comparatively few laboratories have fully mastered. With the partial exception of α-monoglycerides there are still no truly reliable methods of determining the purity of intermediate and final products, although some chromatographic and infrared procedures are promising in this respect. Determinations of saponification equivalents, iodine numbers, and of carbon and hydrogen content have only a limited value, and melting points are by no means conclusive. Thus melting points differing by as much as 5–6°C. have been reported recently for some glycerides (α-stearyl-α'-olein, α,β-dimyristin, α-oleyldistearin, and α-palmityldielaidin) by reputable investigators.

Despite these limitations, and although no radical changes in the methods of glyceride preparation have occurred during the period under review, a measure of progress has been achieved. This progress can be summarized as follows:

1. The range of pure synthetic glycerides has been extended to cover those containing one or more unsaturated acids.
2. Compounds unobtainable by previous methods, such as the β-monoglycerides of unsaturated acids, have been prepared for the first time.
3. The synthesis of pure glycerides has been effected without recourse to blocking by means of "directed interesterification" or by utilizing the different reactivity of the primary and secondary hydroxyl groups of glycerol.
4. Several new glycerides containing short-chain fatty acids such as acetic acid have been prepared, and their properties have been studied with the view to practical application.

The last two developments might be described as a "back to Berthelot move-

ment," inasmuch as the originator of the chemistry of synthetic glycerides employed exclusively direct esterification methods (17) and stressed the fertility of glyceride synthesis as extending beyond the mere reproduction of natural fats (18).

III. PREPARATION OF CHLORIDES OF FATTY ACIDS

Pure glycerides are prepared as a rule from chlorides of fatty acids. As a result of a systematic investigation of various chlorinating agents Bauer (11) concluded that phosphorus tri- and pentachlorides are superior to other reagents for the preparation of chlorides of saturated fatty acids, but that chlorides of unsaturated fatty acids are best prepared by using oxalyl chloride. The same author developed also a convenient method of estimating unreacted fatty acids, based on the conversion of fatty acid chlorides into anilides. Bauer's results with oxalyl chloride are in agreement with the findings of other investigators (152), according to which oleyl, elaidyl, linoleyl, and linolenyl chlorides can be successfully prepared with this reagent with a minimum rearrangement of double bonds. Oxalyl chloride has been also used with great success for the preparation of chlorides of saturated fatty acids, but its high price has led various investigators to use the much cheaper thionyl chloride, which was found quite satisfactory for this purpose. The use of thionyl chloride for the preparation of chlorides of unsaturated acids offers difficulties owing to the formation of tarry products. According to Verkade (143) this can be avoided by purifying thionyl chloride by distillation over quinoline and linseed oil. Still more effective is the use of theoretical amounts of thionyl chloride in the presence of an equimolar quantity of pyridine in an organic solvent (75), which reduces considerably the time and temperature of the reaction.

Crude chlorides of fatty acids are usually purified by distillation *in vacuo*. By an improved distillation technique (31) the yields of 56–89 per cent reported by Bauer (11) for some preparations could be improved to 89–98 per cent. Further improvements, including dispensing with the distillation of the crude acid chlorides, have been suggested very recently (153). The fatty acids are dissolved in 10 volumes of solvent (benzene, Skellysolve F, or carbon tetrachloride) and refluxed with an excess of phosphorus tri- or pentachloride. The excess of the chlorinating agent is removed by washing with water. Quantitative recoveries of acid chlorides with only 1–2 per cent of free acid (estimated by a rapid infrared technique) are claimed. Phosphorus pentachloride is more efficient than the trichloride.

The use of phosgene as chlorinating agent in the presence of a tertiary amine as catalyst (138) or without a catalyst (124) does not seem to hold great promise as a laboratory method.

IV. SYNTHESIS OF MONOGLYCERIDES

A. α-Monoglycerides

The classical monoglyceride synthesis from isopropylideneglycerol (acetoneglycerol) (60) still remains the most reliable method, although recently some doubts have been raised as to the purity of the products thus obtained (125).

Since α-monoglycerides form the basis of the glyceride synthesis, there have been several suggestions in the past aiming at the simplification of the original acetoneglycerol procedure. Recently it has been suggested (118) that acetone be condensed with glycerol in the presence of *p*-toluenesulfonic acid, removing the water formed by azeotropic distillation with light petroleum. It has been also suggested that the fatty acid be introduced by interesterification with a fatty acid methyl ester in the presence of lead oxide instead of the usual acylation with an acid chloride. This modification might have some merit. On the other hand, the proposal to use glycerol formal (obtained by the condensation of formaldehyde with glycerol) instead of acetoneglycerol is apparently impractical because of the difficulty of hydrolyzing this compound after acylation (83).

No other blocking technique for preparing α-monoglycerides has acquired an importance comparable with that of the acetoneglycerol method. Ditritylglycerol[1] according to Verkade (144), a recognized authority on trityl compounds, is inferior as starting material to acetoneglycerol. The oxidation of allyl esters with potassium permanganate to form monoglycerides has been revived (142), but the purity of the products was only about 90 per cent owing to side reactions.

The interesterification of fats with glycerol has been shown (52) to proceed substantially according to chance, producing a random mixture of mono-, di-, and triglycerides. A similar study was carried out recently of the mechanism of the reaction between fatty acids and glycerol (10a). Many suggestions have been made to increase the proportions of monoglycerides in the final mixture by increasing the intersolubility of reagents with the aid of cosolvents and by selecting favorable reaction conditions. Dioxane (24, 128), tertiary aromatic bases (108, 109), and tertiary butyl alcohol (140) are some of the proposed solvents. High yields of monoglycerides are claimed when soaps of iron, nickel, chromium, or manganese (148) are used as catalysts, although the reasons for such behavior are not clear. These and similar procedures produce monoglycerides of 80–90 per cent purity. Heating for 2 hr. at 140–160°C. with a large excess of glycerol has been found to favor the formation of monoglycerides of fatty acids from castor oil (141a). Liquid-liquid extraction of monoglycerides by solvent mixtures such as ethanol–hexane (53) or ethanol–heptane (63), fractional crystallization from mixed solvents (53), and single-solvent extraction (114) have been applied to technical monoglycerides. Further, molecular distillation (92, 141, 149) was reported to yield products with about 90 per cent monoester content.

Eckey's "directed interesterification" (30a, 48), according to which natural fats can be segregated into saturated and unsaturated triglycerides, has been modified to produce monoglycerides and diglycerides of high purity (49). According to this procedure mixtures of triglycerides and glycerol are subjected in the presence of a highly active catalyst (sodium methoxide) to an interesterification process combined with simultaneous fractional crystallization. There is a strong tendency for mono- and diglycerides to precipitate in preference to triglycerides; depending on the amount of added glycerol the precipitated glyceride is either practically pure monoglyceride or diglyceride. Interesterification of cottonseed

oil with 10 per cent of glycerol led, for instance, to the precipitation of an almost pure α-monopalmitin. The method has been used with good results for the preparation of various α-monoglycerides (81). Direct esterification of fatty acids with an excess of glycerol (ten times the theoretical quantity) in a homogeneous medium had been known to produce essentially α-monoglycerides. The reaction between chlorides of fatty acids and an excess of glycerol in a homogeneous medium has been recently made possible by the use of *N*,*N*-dimethylformamide as cosolvent (70). The formation of diglycerides in the course of this reaction was inhibited by complexing glycerol with compounds such as potassium thiocyanate (72). This and similar syntheses are based on the differing reactivities of the primary and secondary hydroxyl groups of glycerol with fatty acids, differences which have been recently reinvestigated and confirmed (115, 116, 117).

Whereas the purity of saturated α-monoglycerides obtained by earlier investigators remained on the whole unsurpassed, the preparation of pure unsaturated monoglycerides was made possible only recently, owing to improved methods of preparing pure unsaturated fatty acids. α-Monoölein, α-monoelaidin, α-monolinolein, and α-monolinolenin (32, 34, 38) have been prepared in high degree of purity and in good yields by the action of the corresponding fatty acid chlorides on acetoneglycerol. α-Monoerucin and α-monobrassidin (25) and α-monoglycerides of chaulmoogric acid [13-(2-cyclopenten-1-yl)tridecanoic acid] and hydnocarpic acid [11-(2-cyclopenten-1-yl)undecanoic acid] (133) have been synthesized in a similar way (67). A fairly pure α-monoölein has been obtained by the interesterification of methyl oleate with glycerol in the presence of an alkaline catalyst, followed by molecular distillation and crystallization from acetone (66).

Following an earlier communication (19) a general method for the preparation of unsaturated mono-, di-, and triglycerides has been suggested by Black and Overley (20), according to which unsaturated acids are first halogenated (preferably brominated), converted to acyl chlorides, esterified by conventional methods, and dehalogenated with zinc. Although it is claimed that this procedure overcomes the danger of configurational changes in unsaturated fatty acids, apparently little use has been made of it in synthetic work.

The thermal data and yields of unsaturated monoglycerides are shown in table 1. It will be noticed that the melting points of both forms I and IV are higher for monolinolenin than for monolinolein, a result which is unexpected. Admittedly the linoleic and linolenic acids used in this synthesis (34) were prepared by the debromination of tetrabromo- and hexabromostearic acids, respectively, but a recent investigation (1) has shown that such acids are practically free from trans isomers and therefore identical, at least in this respect, with those occurring in nature.

The thermal data on three hydroxy acid monoglycerides prepared by an undisclosed method (84), of α-monoarachidin (134) apparently prepared for the first time, and of α-monobehenin (13) are also shown in table 1.

The work on the synthesis of optically active monoglycerides reviewed some years ago in this Journal (61) has been continued and a series of L-α-mono-

TABLE 1

Some recently synthesized α-monoglycerides

Acid Radical	Melting and Transition Points				Yield	Reference
	Form I	Form II	Form III	Form IV		
	°C.	°C.	°C.	°C.	*per cent*	
Oleic	35.0	32.0	25.0	12.5	47.5	(25)
Elaidic	58.5	56.0	42.0	29.5	63.4	(25)
Erucic	50.0	47.0	36.0	15.0	72.2	(25)
Brassidic	71.0	68.5	62.0	37.0	65.6	(25)
Linoleic	12.3	—	—	−22.8		(34)
Linolenic	15.7	—	—	−13.5		(34)
Hydnocarpic	49.0	47.0	39.5		69.4	(67)
Chaulmoogric	58.5–59.0	57.5	53.5		67.0	(67)
Arachidic	83.5	81.5	77.0			(134)
12-Hydroxystearic	67; 88					(84)
9,10-Dihydroxystearic	124.0					(84)
9,10,12-Trihydroxystearic	91; 125					(84)
Behenic	87.2					(13)

TABLE 2

Characteristics of L-*α-monoglycerides*

Acid Radical	Melting Point	M_D	Yield	Reference
	°C.		*per cent*	
Acetic		14.07	94.0	(5)
Propionic		13.32	95.0	(5)
Butyric		13.44	43.0	(5)
n-Valeric		13.73	61.5	(5)
Isovaleric		12.85	62.3	(5)
Caproic	7–9	14.63	47.5	(5)
Enanthic	14–15	14.89	49.0	(5)
Caprylic	28–30	14.38	57.0	(5)
Pelargonic	34–35	14.61	47.0	(5)
Capric	44	13.78	82.5	(5)
Hendecanoic	49–50	14.04	80.6	(5)
Lauric	54–55	13.43	57.0	(5)
Myristic	62–64	13.89	85.0	(5)
Palmitic	71–72	14.52	73.0	(5)
Stearic	76–77	12.89	56.0	(5)

glycerides containing C_2 to C_{18} acids with the exception of C_{13}, C_{15}, and C_{17} members has been prepared (5). As in previous investigations, the monoglycerides were produced by the acylation of D(+)-acetoneglycerol and acid hydrolysis of the acetone compounds. The hydrolysis of the lower members (up to C_8) was carried out with 10 per cent acetic acid at 60°C., whereas the higher members were hydrolyzed with concentrated hydrochloric acid at temperatures ranging from −40°C. to −15°C. The characteristics and yields of the products are shown in table 2.

B. β-Monoglycerides

The importance of β-monoglycerides is illustrated by the fact that substantial amounts of unsaturated monoglycerides of this type are present in intestinal contents (112), and that commercial monoglycerides invariably contain the β-isomer (23).

TABLE 3

β-Monoglycerides

Acid Radical	Melting Point	Reference	Acid Radical	Melting Point	Yield	Reference
	°C.			°C.	*per cent*	
Saturated:			Unsaturated:			
Caproic	−8 to −10	(37)	Oleic	23.5	58	(106)
Caprylic	29.8	(37)	Elaidic	54.2		(106)
Capric	40.4	(57)	Linoleic	8.9	30	(106)
Lauric	51.0	(57)				
Myristic	61.2	(57)				
Palmitic	68.5	(57)				
Stearic	74.5	(57)				

The starting material in the synthesis of saturated β-monoglycerides is α,α′-ditritylglycerol or preferably α,α′-benzylideneglycerol, the preparation of which has been described more recently by Verkade and van Roon (147). After acylation the blocking group is removed by hydrogenolysis. However, this last step prevents the application of the method to the synthesis of unsaturated β-monoglycerides, since regardless of the conditions of hydrogenation a fully saturated glyceride is always obtained (33), whereas acid hydrolysis results in the acyl shift from the β- to the α-position. This difficulty has been recently overcome by Martin (106) with the use of boric acid.

Boric acid displaces the labile benzylidene group from the benzylideneglycerol ester with simultaneous esterification of the free hydroxyl groups at temperatures not exceeding 100°C., especially if triethyl borate is used as solvent. The borate esters are readily hydrolyzed with water to yield β-monoglycerides. Saturated β-monoglycerides can also be prepared by this method, and better yields are claimed than those obtained with the conventional method. Table 3 shows the constants of unsaturated β-monoglycerides and also data on several saturated β-monoglycerides prepared by the hydrogenolysis of benzylidene compounds (37, 57), some of them for the first time.

Isomerization of α- and β-monoglycerides with 56 per cent aqueous perchloric acid in chloroform solution (107) has shown the existence of an equilibrium in the composition range of 90–92 per cent of the α-isomer and 8–10 per cent of the β-isomer. This has been confirmed in the case of commercial monoglycerides (23), and it is possible that β-monoglycerides are widespread and occur in concentrations higher than hitherto believed.

V. SYNTHESIS OF DIGLYCERIDES

A. α,α′-Diglycerides

Developments in the synthesis of α,α′-diglycerides comprise: (*1*) the preparation of pure diglycerides with one and two unsaturated acid components by the use of the trityl technique (42, 43, 44) and by direct acylation of α-monoglycerides (16, 25, 29, 42, 45, 66, 67); (*2*) the synthesis of saturated diglycerides with the aid of new blocking techniques (10, 123, 131); and (*3*) the preparation of simple diglycerides by modified "directed interesterification" (14, 15, 49) and by the direct acylation of glycerol (27, 72, 129).

TABLE 4

α,α′-Diglycerides with one and two unsaturated acid components

Glyceride	Transition or Melting Point			Yield (Based on Acid Chloride)	Proof of Structure	Reference
	Form I	Form II	Form III			
	°C.	°C.	°C.	*per cent*		
Diolein	25.0	20.0	0.0			(66)
Dielaidin	55.0	53.0	49.0	Approximately 70		(25)
Dierucin	46.5	44.5	41.0	Approximately 70		(25)
Dibrassidin	68.5	66.5	63.5	Approximately 70		(25)
Dilinolein	−2.6				Hydrogenation	(43)
Dilinolenin	−12.3				Hydrogenation	(43)
Dihydnocarpin	49.0	47.0	42.0	50		(67)
Dichaulmoogrin	59.0	57.0	52.0	57		(67)
Laurylolein	32.0				Hydrogenation	(42)
Myristylolein	41.0				Hydrogenation	(42)
Palmitylolein	46.0				Hydrogenation	(42)
Stearylolein	54.0				Hydrogenation	(42)
	54.0					(45)
	49.0					(29)
Elaidylolein	28.8				Hydrogenation	(16)
Stearylelaidin	65.5–65.9				Hydrogenation	(16)

The trityl technique and the direct acylation of α-monoglycerides may be used for the preparation of both simple and diacid diglycerides, whereas the modified "directed interesterification" and direct acylation of glycerol produce simple diglycerides only. Two modifications of the trityl technique are employed, depending on the type of diglycerides required. For the preparation of simple diglycerides the starting material is the α-monotrityl ether of glycerol, which is acylated with two moles of an acid chloride, whereupon the trityl group is removed. Diacid diglycerides are prepared by the tritylation of α-monoglycerides, introduction of a second acyl group, and removal of the blocking group. Another proven method of synthesizing diglycerides based on the acylation of glycerol α-iodohydrin (59) has not been lately in use, owing to the unavailability of iodohydrin.

The trityl method involves an acyl shift from the β- to the α′-position, which does not occur in direct acylation procedures and in most of the new blocking techniques to be described.

Table 4 shows the thermal data and other characteristics of diglycerides with one and two unsaturated acid components obtained by the "trityl" method or by the direct acylation of α-monoglycerides. It will be noted that the melting point of α-stearyl-α′-olein prepared by the direct acylation (29) of α-monostearin is 5°C. lower than those of two other preparations (41, 45), one of which was obtained by the same method. This emphasizes the difficulty of determining accurately the thermal properties of some synthetic glycerides. Three other instances of this kind are shown in tables 6 and 9.

New blocking techniques suggested recently for the synthesis of α,α′-di-

glycerides are interesting more on theoretical grounds than as preparative procedures, since they require more steps than conventional methods.

One of them (131) is based on a successive building up of alcoholic groups of glycerol according to the following reactions (R = an alkyl group):

$$RCOOCH_2COCl \xrightarrow{CH_2N_2} RCOOCH_2COCHN_2 \xrightarrow{H^+}$$

$$RCOOCH_2COCH_2OH \xrightarrow[(3)\ HBr]{(1)\ H_2SO_4,\ (2)\ K_2CO_3} RCOOCH_2COCH_2Br \xrightarrow{RCOOK}$$

$$RCOOCH_2CCOH_2OCOR \xrightarrow[Ni]{H_2} RCOOCH_2CHOHCH_2OCOR$$

By labelling the glycerol carbon atoms during the synthesis and using a radioactive fatty acid a detailed structural knowledge of the glyceride could be obtained.

A modified procedure of synthesizing simple α,α'-diglycerides from dihydroxyacetone (10) includes the protection of the ketone group as mercaptal to avoid dimerization, acylation with propionic anhydride, and interesterification of the α,α'-dipropionoxyacetone diethylmercaptal thus obtained with methyl esters of long-chain fatty acids. The mercaptan is removed with mercuric chloride, and the ketone group is reduced in the presence of Raney nickel.

Another example of preparing simple α,α'-diglycerides without an acyl shift is provided by the following procedure (123), which uses α,α'-benzylideneglycerol as starting material. The remaining free hydroxyl group of this compound is protected with a benzyl group, the benzylidene block is removed by acid hydrolysis, and the β-benzylglycerol is acetylated. The long-chain fatty acids are introduced by interesterification in the presence of sodium methoxide (85 per cent yields), whereupon hydrogenolysis produces the α,α'-diglycerides (yield 97–98 per cent). The melting points of dipalmitin (73.5°C.) and distearin (80°C.) obtained by this method were slightly higher than those reported for preparations by the trityl method (72.5°C. and 79.5°C., respectively) (79).

The use of allyl alcohol as starting material has also been suggested (10). An ether is formed with 2,3-dihydropyran, followed by oxidation with potassium permanganate to α-tetrahydropyranylglycerol, acylation of the β,α'-hydroxyl groups, and removal of the blocking group by acid hydrolysis. There appears to be no advantage over the trityl method.

Glycidyl esters have been reported (76, 85) to react smoothly with fatty acids at about 130°C. with the formation of α,α'-diglycerides. α-Lauryl-α'-stearin (m.p. 62–64°C., yield 25 per cent) and α-erucyl-α'-stearin (m.p. 56–57°C., yield 40 per cent) have been prepared by this method. In conjunction with the preparation of glycidyl esters from epichlorohydrin and sodium soaps (86, 87), this would provide a general method for the preparation of both α-mono-

TABLE 5

α,α′-Diglycerides prepared by modified directed interesterification

Glyceride	Melting Point	Yield	Crystallization Temperature		Reference
			Initial	Final	
	°C.	*per cent*	°C.	°C.	
Dilaurin	57.8	72	32	16	(15)
Dimyristin	66.8	81	32	16	(15)
Dipalmitin	74.2	86	46	27	(15)
Dimargarin	76.3	86	46	27	(15)
Distearin	79.4	80	46	27	(15)
Dibehenin	87.6	87	60	38	(15)
Dielaidin	54.4	70	32	10	(15)

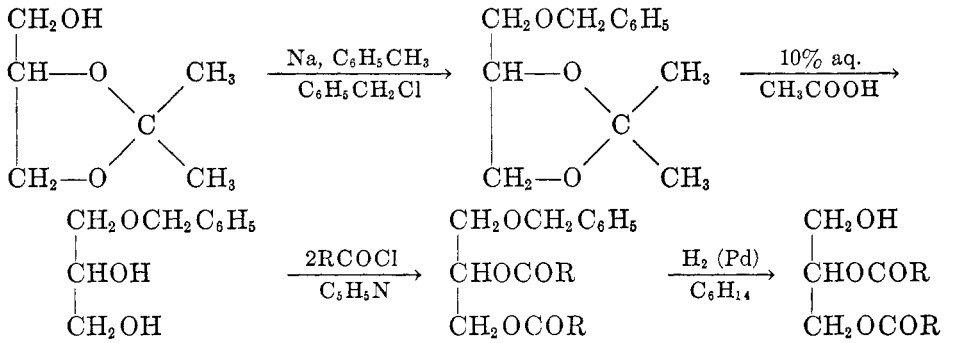
glycerides (by the acid hydrolysis of glycidyl esters) and α,α′-diglycerides, but the procedure is time-consuming and not devoid of difficulties.

As mentioned in the section on α-monoglycerides, the modified "directed interesterification" of fats results in the formation of diglycerides if the reaction is carried out in the presence of suitable proportions of glycerol (14, 49). Natural fats containing principally one kind of saturated acid may be used, but better yields and purer products are obtained if mixtures of simple triglycerides and triacetin are interesterified and progressively crystallized (15). The initial and final temperatures of crystallization and the melting points of diglycerides thus obtained are shown in table 5. With the exception of dielaidin and distearin the melting points are the highest ever reported.

Direct esterification of glycerol with chlorides of fatty acids has also been used to prepare α,α′-diglycerides. Dipalmitin (m.p. 73.0–73.5°C., yield 64 per cent) was obtained by reacting a mixture of glycerol and quinoline with a solution of palmityl chloride in chloroform at 10–15°C. (129). More recently (27) dilaurin (m.p. 56.5°C.), dipalmitin (73.5°C.), and distearin (78.7°C.) were obtained by the same method. By carrying out the reaction at room temperature in a solution obtained by the addition of *N*,*N*-dimethylformamide (72), dipalmitin (m.p. 73.5–74°C., yield 67 per cent) and distearin (m.p. 80°C., yield 72 per cent) were prepared. The high melting points of the final products indicate that there is no appreciable formation of triglycerides under these conditions.

B. α,β-Diglycerides

The preparation of α,β-diglycerides by the hydrogenolysis of α,β-diacyl-α′-tritylglycerol (146) has been extended to diglycerides with two component acids (145), such as α-palmityl-β-stearin and α-stearyl-β-palmitin. However, the best method for the preparation of α,β-diglycerides, especially with one component acid, seems to be that employed by Howe and Malkin (74), which is a modification of the procedure of Sowden and Fischer for the synthesis of optically active α,β-diglycerides (139). It is illustrated by the following reactions:



The method can be adapted to the preparation of α,β-diacid diglycerides by carrying out a two-stage direct acylation of α-benzylglycerol.

The melting points of various preparations of α,β-diglycerides are shown in table 6.

Sowden and Fischer's original method (139) was used by its authors for the preparation of optically active α,β-dibutyrin, α,β-dipalmitin, and α,β-distearin from D(+)-acetoneglycerol. Owing to the need for distilling D(+)-α,β-dibutyrin, a process which could induce some racemization, this compound

TABLE 6

α,β-Diglycerides

Glyceride	Melting Point		Yield (Based on Acid Chloride)	Proof of Structure	Reference
	Form I	Form II			
	°C.	°C.	*per cent*		
Dilaurin	39.0	20.0	62.4		(74)
Dimyristin	54.0	37.5	66.4		(74)
	59.0				(39)
Dipalmitin	63.5	50.0	81.8		(74)
Distearin	71.0	59.5	70.6		(74)
α-Stearyl-β-palmitin	68.5–69.5		83.7	Conversion to β-palmityldistearin	(145)
α-Palmityl-β-stearin	60.5–61.0		83.7	Conversion to α-palmityl-β-stearyl-α'-tritylglycerol	(145)

TABLE 7

Optically active α,β-diglycerides

Glyceride	Melting Point	Yield (Based on Acid Chloride)	Reference
	°C.	*per cent*	
D-α,β-Dibutyrin		60.2	(139)
D-α,β-Dimyristin	58–59	35.5	(6)
L-α,β-Dimyristin	58–59	58.5	(7)
D-α,β-Dipalmitin	67–67.5	64.1	(139)
	68–69		(6)
D-α,β-Distearin	74.5–75	52.5	(139)
	76–77		(6)

might not have been optically pure. By an essentially similar method D-α,β-dimyristin (6) and L-α,β-dimyristin (7) have been prepared. The characteristics of all these products are shown in table 7.

The above-mentioned methods involve hydrogenolysis and therefore cannot be used for the synthesis of unsaturated α,β-diglycerides. It appears, however, that the preparation of D- and L-α,β-diolein has now been accomplished (3); this represents a major advance in glyceride synthesis.

VI. SYNTHESIS OF TRIGLYCERIDES

A. Simple triglycerides

Whereas saturated triglycerides, both simple and mixed, had been prepared in a high degree of purity by earlier investigators, the synthesis of pure triglycerides containing one or more unsaturated acids was delayed until these acids became available in a sufficiently pure state. Certain procedural difficulties due to the instability of unsaturated acids had also to be overcome. Although such a comparatively simple triglyceride as triolein has been prepared by a variety of methods during the last hundred years, its first really satisfactory preparation (as well as that of trilinolein) was accomplished in 1940 (151). The method consisted in esterifying glycerol directly with pure oleic acid in an inert atmosphere with *p*-toluenesulfonic acid as catalyst. (Incidentally, the esteraselike action of various alkylarylsulfonic acids was the subject of a recent comprehensive study (1a).)

Triglycerides of other unsaturated acids were obtained later by the acylation of glycerol with the corresponding fatty acid chlorides (34, 113) and by the esterification of α-monoglycerides with fatty acids *in vacuo* at 100°C. in the presence of acid catalysts (25) or with fatty acid chlorides in the presence of pyridine (25, 67). Their characteristics are shown in table 8.

Triglycerides in about 70 per cent yield may also be prepared by the interesterification of methyl or ethyl esters of fatty acids with glycerol in the presence of alkaline catalysts (64, 83). The interchange between the above esters and triacetin in the presence of sodium alkoxide (64, 88) provides another means

TABLE 8

Simple triglycerides of unsaturated acids

Glyceride	Transition Point				Reference
	Form I	Form II	Form III	Form IV	
	°C	°C.	°C.	°C.	
Triolein	5.5	−13.0	−32.0	—	(51)
Trielaidin	42.0	—	37.0	15.5	(25)
Tripetroselaidin	52.5	—	18.8	—	(113)
Trierucin	30.0	25.0	17.0	6.0	(25)
Tribrassidin	59.0	—	50.0	43.0	(25)
Trilinolein	−12.9	—	−45.6	—	(34)
Trilinolenin	−24.2	—	−44.6	—	(34)
Trihydnocarpin	34.0	31.0	24.0	15.0	(67)
Trichaulmoogrin	44.5	41.5	35.0	27.0	(67)

of obtaining triglycerides, and pure trieleostearin, unobtainable by the direct esterification of eleostearic acid owing to gelation, has been prepared by this method (88). Since methyl esters are purified more easily than fatty acids, the above-mentioned methods seem to offer certain advantages from the standpoint of cost and simplicity, especially in the preparation of large samples.

B. Diacid triglycerides

Here again it was the preparation of triglycerides with one or more unsaturated acid components which presented problems. In particular, difficulty is experienced in the introduction of the third acyl group into the molecule, whether this acyl group be saturated or unsaturated. At room temperature the reaction with acid chlorides does not proceed beyond the diglyceride stage, as has been noticed by earlier investigators (2) and repeatedly confirmed later. Only by maintaining the reaction mixtures at 50–80°C. for several hours is it possible to obtain satisfactory yields (40).

It has been suggested (104) that even under these conditions a certain amount of diglyceride escapes acylation, and that the only method of obtaining a pure final product is to use an extravagant excess of acid chloride (about four times the theoretical quantity) at about 80°C. Although this procedure has proved successful, the use of such an excess of compounds as reactive as acid chlorides at elevated temperatures presents the danger of side reactions. A moderate excess of acid chloride (5–10 per cent) and the removal of residual diglycerides by chromatography on alumina (29) appears more satisfactory.

It seems that the difficulty is connected primarily with the cis-configuration, because Bömer and Kapeller succeeded in preparing α-palmityldielaidin and α-stearyldielaidin at room temperature (21). It may be a case of steric hindrance, which would be less pronounced with trans acids.

Triglycerides containing an unsaturated acid in the α-position have been prepared by refluxing a chloroform solution of an unsaturated α-monoglyceride with two moles of a saturated acid chloride in the presence of quinoline or pyridine. The unsaturated α-monoglycerides were monoölein (38, 96), monolinolein (35), and monoelaidin (32). Conversely, α-saturated-β,α'-unsaturated glycerides were prepared from saturated α-monoglycerides and chlorides of unsaturated fatty acids in chloroform–pyridine solution under reflux conditions (32, 35, 45, 113).

Symmetrical diacid triglycerides with an unsaturated or a saturated acid in the β-position were obtained by the reaction of α,α'-diglycerides with appropriate (unsaturated or saturated) acid chlorides (79, 100, 104, 113).

All these types of triglycerides are listed in table 9. Certain anomalies regarding molecular weight determinations, refractive indices, and melting points of some of the series have been discussed by Daubert and Longenecker (41).

The melting points of two preparations of α-palmityldielaidin differ by 6°C. It was pointed out that the lower melting point was not due to a metastable polymorph (113).

Special thermal and diffraction characteristics are exhibited by diacid tri-

TABLE 9

Diacid triglycerides containing one or two unsaturated acid components

Glyceride	Melting Point					Proof of Structure	References
	Form I	Form II	Form III	Form IV	Form V		
	°C.	°C.	°C.	°C.	°C.		
α-Oleyldicaprin	5.3	−2.5	−15.0	−27.0		Hydrogenation to α-stearyldiacylins	(36,38)
α-Oleyldilaurin	15.5	4.8	−10.0	−15.5		Hydrogenation to α-stearyldiacylins	(36,38)
α-Oleyldimyristin	25.0	22.7	18.6	3.8		Hydrogenation to α-stearyldiacylins	(36,38)
α-Oleyldipalmitin	34.5	—	29.8	18.5		Hydrogenation to α-stearyldiacylins	(36,38)
α-Oleyldistearin	38.5	—	—	26.7		Hydrogenation to α-stearyldiacylins	(36,38)
	43.5	42.5	—	30.4			(96)
α-Elaidyldicaprylin	3.0					Hydrogenation	(32)
α-Elaidyldicaprin	15.0					Hydrogenation	(32)
α-Elaidyldilaurin	27.0					Hydrogenation	(32)
α-Elaidyldimyristin	39.5					Hydrogenation	(32)
α-Linoleyldicaprylin	−13 to −12					Hydrogenation	(35)
α-Linoleyldicaprin	−1 to 0					Hydrogenation	(35)
α-Linoleyldilaurin	15–16					Hydrogenation	(35)
α-Linoleyldimyristin	20–21					Hydrogenation	(35)
α-Linoleyldipalmitin	26–27					Hydrogenation	(35)
α-Linoleyldistearin	32–33					Hydrogenation	(35)
α-Caproyldiolein	−14.5		−34.2	−56.5		Hydrogenation	(36,45)
α-Caprylyldiolein	−18.5			−50.0		Hydrogenation	(36,45)
α-Capryldiolein	−0.6		16.5	−40.5		Hydrogenation	(36,45)
α-Lauryldiolein	4.3		−10.9	−32.0		Hydrogenation	(36,45)
α-Myristyldiolein	13.3		−4.2	−21.8		Hydrogenation	(36,45)
α-Palmityldiolein	15.8		2.5	−13.2		Hydrogenation	(36,45)
α-Stearyldiolein	22.9		8.6	−1.5		Hydrogenation	(36,45)
α-Lauryldilinolein	−12 to −11					Hydrogenation	(35)
α-Myristyldilinolein	−9 to −8					Hydrogenation	(35)
α-Palmityldilinolein	−4 to −3					Hydrogenation	(35)
α-Stearyldilinolein	5–6					Hydrogenation	(35)
α-Capryldielaidin	25.0					Hydrogenation	(32)
α-Lauryldielaidin	35.5					Hydrogenation	(32)
α-Myristyldielaidin	40.0					Hydrogenation	(32)
α-Palmityldielaidin	46.0					Hydrogenation	(32)
	40.3	33.0		22.8			(113)
α-Palmityldipetroselaidin	46.4	35.9		26.4			(113)
α-Stearyldipetroselaidin	55.0			31.5			(113)
β-Oleyldicaprin	5–6					Hydrogenation	(79)
β-Oleyldilaurin	14.5–15					Hydrogenation	(79)
β-Oleyldimyristin	28.5	26.5	19.0	11.0	2.0		(104)
β-Oleyldipalmitin	37.5	35.0	29.0	21.5	12.0		(104)
β-Oleyldistearin	43.5	41.5	37.0	29.5	23.0		(104)
β-Elaidyldipalmitin	55.0	52.5	—	42.0	33.0		(104)
β-Elaidyldistearin	61.0	58.0	—	46.0	40.0		(104)
β-Petroselaidyldipalmitin	54.9	54.3		35.9			(113)
β-Petroselaidyldistearin	62.6			43.4			(113)
β-Palmityldielaidin	44.5	32.0		26.0			(113)
β-Stearyldielaidin	50.1	43.2		34.0			(113)

TABLE 10

Diacid triglycerides containing C_2–C_6 or C_{22} fatty acids

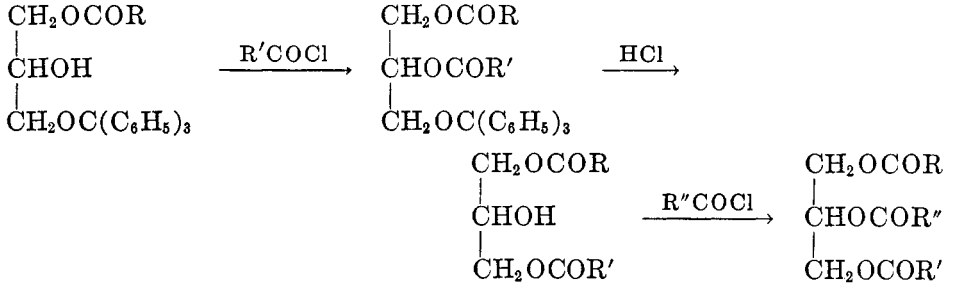
Glyceride	Melting Point	Reference	Glyceride	Melting Point	Reference
	°C.			°C.	
α,β-Diacetylpalmitin	22.4	(81)	β-Butyryldistearin	54.8	(82)
α,β-Diacetylstearin	34.1	(81)	β-Caproyldipalmitin	44.5	(82)
α,β-Diacetylbehenin	53.1	(13)	β-Caproyldistearin	53.1	(82)
α,β-Dipropionylstearin	23.5	(81)	β-Palmityldiacetin	37.0	(98a)
α,β-Dibutyrylpalmitin	2.9	(81)	β-Stearyldiacetin	43.5	(98a)
α,β-Dibutyrylstearin	15.6	(81)	α,β-Diacetylolein	−17.5	(66)
α,β-Dicaproylpalmitin	−7.4	(81)	α,β-Dibutyrylolein	−29.0	(66)
α,β-Dicaproylstearin	6.0	(81)	β-Behenyldipalmitin	47.4	(80)
β-Acetyldipalmitin	54.8	(82)	β-Behenyldistearin	56.0	(80)
β-Acetyldistearin	62.8	(82)	α-Palmityldibehenin	55.9	(80)
β-Butyryldipalmitin	46.5	(82)	α-Stearyldibehenin	61.3	(80)

glycerides containing very short (C_2 to C_6) or unusually long (C_{22}) fatty acid chains. A number of such glycerides have been prepared by conventional methods (acylation of α-monoglycerides and α,α′-diglycerides, respectively), some of them for the first time (66, 78, 80, 81, 82). These glycerides are listed in table 10. Because of the great variety of modifications the highest melting points only are shown, and the original papers should be consulted for details.

Monoacyldiacetins have been also obtained by the interesterification of natural fats and triacetin in the presence of sodium methoxide, followed by fractional distillation and hydrogenation (12, 13). Several acetostearins and acetoöleins with different degrees of acetylation have been recently prepared from the corresponding α-monoglycerides and acetic anhydride (54, 55, 56). It seems that all these products have a future as plasticizers and coatings in the food and other industries (12, 65, 78, 93).

C. Triacid triglycerides

In principle any triacid triglyceride of saturated long-chain acids is obtainable by the trityl method according to the following scheme (R = an alkyl group):



By varying the kind of α-monoglyceride and the sequence of acylation the three possible isomers of a given triglyceride may be prepared. Using α-monostearin as starting material Chen and Daubert (30) prepared by this method four groups of isomeric glycerides containing C_{10} to C_{18} acids. Some of these

TABLE 11

Saturated triacid triglycerides

Glyceride	Transition Point			Reference
	Form I	Form II	Form III	
	°C.	°C.	°C.	
Myristyllaurylcaprin	36.5–37.0	33–34	22.0	(136)
Palmitylmyristyllaurin	48.5–49.0	44.0	36–37	(136)
Stearyllaurylcaprin	44.0	40.0	14.5	(30)
Stearylmyristylcaprin	45.0	42.0	21.5	(30)
Stearylpalmitylcaprin	50.0	46.5	26.1	(30)
Stearylcapryllaurin	41.8	—	22.3	(30)
Stearylmyristyllaurin	49.5	45.5	27.5	(30)
Stearylpalmityllaurin	52.0	47.0	33.4	(30)
Stearylcaprylmyristin	52.5	50.1	14.0	(30)
Stearyllaurylmyristin	55.0	51.9	28.8	(30)
Stearylpalmitylmyristin	58.5	56.0	40.3	(30)
Stearylcaprylpalmitin	55.0	53.8	20.1	(30)
Stearyllaurylpalmitin	57.5	56.0	32.0	(30)
Stearylmyristylpalmitin	59.5	56.1	40.6	(30)

glycerides displayed an unusual behavior, inasmuch as they did not crystallize from solvents in their highest-melting modification without being equilibrated at 25°C. for 12 hr. or more. Their characteristics and those of two other glycerides prepared by Sidhu and Daubert (136) are shown in table 11.

If one of the component acids is of low molecular weight or unsaturated, and therefore has a low melting point, complications arise, since α,β-diacyl-α'-trityl intermediates containing such an acid are difficult to obtain in a pure state and in good yields. Incidentally this difficulty was evident in the synthesis of unsaturated α,α'-diglycerides by the trityl method (42).

To avoid this difficulty, Verkade (143) used α,β-diglycerides of high-melting acids as intermediates in the preparation of the two isomeric triglycerides containing a low-melting acid in the α'-position. The third isomer with the low-melting acid in the β-position was obtained from α,α'-diglycerides of high-melting acids. Thus in each case the low-melting component was introduced in the final step. Proceeding in this way, three isomeric butyrylpalmitylstearins and oleylpalmitylstearins were prepared. The isomeric oleylpalmitylstearins have also been prepared recently from α,α'-diglycerides obtained by direct acylation (29, 72), a procedure which is much simpler, although perhaps less satisfactory from the theoretical point of view.

The characteristics of the products, including thermal data determined on some of them by Lutton (96), appear in table 12.

The earlier observation (4) that enantiomorphic triglycerides containing only aliphatic acid residues do not possess a detectable optical rotation has been confirmed (137, 139), although no extensive work has been carried out on this subject. It is characteristic that even the acetylation of D(+)-α,β-distearin (139) led to the disappearance of the optical activity, whereas the methanesulfonyl derivative (8) was optically active. There seems to be little doubt that the lack of measurable optical activity in most natural fats does not pre-

TABLE 12

Triacid triglycerides with a low-melting fatty acid component

Glyceride	Melting or Transition Point			Yield (Based on Diglyceride)	Reference
	Form I	Form II	Form III		
	°C.	°C.	°C.	*per cent*	
Stearylpalmitylbutyrin	47.5–48.0			87	(143)
Palmitylstearylbutyrin	49.5–50.0			91	(143)
Palmitylbutyrylstearin	45.5–46.0			87	(143)
Stearylpalmitylolein	40.0–41.0			86	(143)
		40.2	25.3		(96)
Palmitylstearylolein	39.5–40.5			84	(143)
		39.8	26.3		(96)
Palmityloleylstearin	36.5–37.5			78	(143)
	37.3	33.0	18.2		(96)
Palmityloleyllaurin	29.5			67	(72)

clude their being enantiomorphs. This might be to some extent responsible for the discrepancy in melting points between synthetic DL-triglycerides and those isolated from natural sources.

VII. CRITERIA OF PURITY AND STRUCTURE

A. Oxidation with periodates

Chemical methods do not provide on the whole a satisfactory measure of purity. As already mentioned, α-monoglycerides are the only glycerides that can be estimated specifically with some degree of accuracy. The two original procedures based on the oxidation of free hydroxyl groups of α-monoglycerides with periodic acid (122) and with sodium periodate (77) have been followed by numerous modifications (47, 50, 69, 71, 89, 121) which make possible the determination of these compounds within 1 per cent in the presence of other glycerides and—in some procedures—of free glycerol. β-Monoglycerides do not react, but by combining periodate oxidation with isomerization with perchloric acid (107), which produces an equilibrium between the two types of monoglycerides, the approximate content of β-monoglycerides can be computed.

B. Chromatographic methods

Chromatography on silica gel was apparently used for the first time by Sidhu and Daubert (135) to determine the homogeneity of synthetic diacid diglycerides. Recently several chromatographic methods have been suggested for the identification and separation of various types of glycerides. A procedure using glass-fiber filter paper impregnated with silicic acid (46) resolves mixtures of α-monoglycerides, α,α'-diglycerides, and triglycerides with the aid of ethyl ether–isoöctane solvent systems and with sulfuric acid as reagent for the detection of spots. Other chromatographic procedures applied to glyceride mixtures include: paper chromatography using various indicators such as α-cyclodextrin and iodine, lead tetraacetate, and lipase (62, 105); oxidation with periodate followed by separation on silicic acid (22); displacement chromatography with charcoal as the absorbent (68); elution chromatography on silica gel (127).

A survey of paper chromatographic procedures investigated in the Hormel Institute at the University of Minnesota (130) contains a number of suggestions for the qualitative and quantitative analysis of glycerides.

Molecular distillation of glycerides *per se* or in conjunction with chromatographic analysis has also been recommended as a general criterion of purity (125).

C. Thermal and x-ray investigation

The work on the thermal and x-ray patterns of glycerides, generally accepted as important criteria of purity and structure (95), has been actively pursued and a large amount of new data has been published. Unfortunately this progress has been accompanied by considerable confusion, owing to the disagreement between leading authorities regarding results and their interpretation (97, 101). In addition to the previously known three modifications of α-monoglycerides, a fourth modification has been reported (99). β-Monoglycerides have been examined for the first time (36, 57) and found to exhibit no polymorphism.

Reëxamination of simple α,α'-diglycerides (14) has shown the existence of two forms only and not of three, as previously reported (103). However, according to Malkin (101) three forms do exist; three modifications have been also found for α,α'-diacid diglycerides (135). The investigation of the polymorphism of α,β-diglycerides (74) disclosed two solid modifications. The polymorphism of the mono- and diglycerides of cis and trans monounsaturated fatty acids (25) was found to be similar to that of the corresponding saturated compounds, but the mono- and diglycerides of linoleic and linolenic acids (34, 43) behaved differently.

The confusion noticeable in the opinions on the polymorphism of mono- and diglycerides is still more pronounced with regard to triglycerides. Whereas Malkin distinguishes four modifications of triglycerides, which include a vitreous form (101), Lutton (94) and other American investigators (9, 58) have denied the existence of the vitreous form but have reported several additional modifications (80, 82). Until these differences are resolved, both the existence and the nomenclature of various modifications remain uncertain.

D. Infrared spectra

The infrared spectroscopy which is finding increasing application to fatty acid derivatives (119, 150) has produced some results of interest to the synthesis of glycerides. The extension of the determination of trans monounsaturated acids by the infrared technique (132) to acids of higher unsaturation has revealed, as mentioned previously, that linoleic and linolenic acids, obtained by the debromination technique, contain only traces of trans isomers (1). This should remove reservations against their use in synthetic work.

Infrared spectra have been used for the identification of monoglycerides in the presence of triglycerides (90, 91) by the "finger-print" technique; further, the spectra of mono-, di-, and triglycerides have been studied (120) with the view of developing analytical procedures. Both qualitative and quantitative

determinations of mixtures of these compounds might be achieved by examining characteristic bonds in the region of 3.0 and 9.0 microns.

In a series of remarkable papers Chapman has described the infrared spectra of α- and β-monoglycerides (26), α,α'-diglycerides and simple triglycerides (27), and diacid triglycerides (28) in relation to their polymorphic transitions. On the whole his results support Lutton's views rather than Malkin's on the polymorphism of the glycerides in question.

E. Conclusive proof of structure

Whereas the structure of mono- and diglycerides can be verified by their conversion into triglycerides, the only dependable proof of the position of fatty acids in isomeric triglycerides is based on the reliability of methods used in their preparation. Mixed triglycerides containing unsaturated acids have usually been identified by hydrogenation and comparison with the corresponding fully saturated compounds (79), but recent investigations of the major component glyceride of cocoa butter (29, 98, 129a) have convincingly demonstrated the inadequacy of any single analytical method for determining the structure of such glycerides. Only by employing several independent methods was it possible to arrive at a definite conclusion on this point; moreover, the most important requisite was the availability of synthetic compounds of known structure for comparative tests. Fortunately the present standard methods based on the use of isopropylideneglycerol, benzylideneglycerol, and tritylglycerol offer means of preparing a wide range of glycerides of known structure. These preparations can serve as standards for comparison with products obtained by less time-consuming, direct esterification methods. Hydrolysis of glycerides with pancreatic lipase has been recently suggested as a means of determining the position of fatty acids in a glyceride molecule on the basis of the specific action of the lipase on the primary hydroxyl group linkages of glycerol (110, 111). Although satisfactory results have been obtained with some glycerides, reports are conflicting and more work is required. In view of the comparatively simple nature of glyceride molecules it is rather remarkable that, with the exception of monoglycerides, for the time being there are no recognized analytical procedures for the establishment of their structure. To some degree this exemplifies the peculiar nature of fat chemistry.

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