# SYNTHETIC FATTY ACID GLYCERIDES OF KNOWN CONSTITUTION[1]

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## I. INTRODUCTION

A reasonably clear picture of the chemical constitution of natural fats and oils is basically dependent upon our knowledge of the molecular structure of the individual components. Because of the many difficulties inherent in isolating the individual glycerides from natural products, only moderate progress has been made in that direction. No doubt such progress will be greatly accelerated by the newer techniques that are being developed, such as molecular distillation in conjunction with fractional crystallization and solvent partition. Nevertheless, the postulated structures of nearly all isolated products will need to be checked against the evidence provided by synthesis, because nearly all of the constituent fatty acids occur as mixed triglycerides which can exist in either of two or more stable isomeric forms. The work in our laboratory has been chiefly of two types: (*a*) studies of satisfactory methods of synthesis, and (*b*) studies of relationships

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between the structure and properties of known isomers.[2] We feel that the synthesis of isomeric mixed triglycerides by reliable methods offers a valuable approach to the study of natural fats and oils, in that such work provides physical and chemical data for identification purposes and also permits correlations between structure and properties from which one can outline procedures for separating anticipated mixtures from natural products.

## II. EARLY WORK ON MIXED TRIGLYCERIDES

Although Chevreul (24), in 1823, concluded that natural fats were primarily glycerol esters of oleic, palmitic, and stearic acids, it remained for Berthelot (13) to point out that they were probably composed of mixed triglycerides rather than mixtures of such simple glycerides as triolein and tristearin. Fritzweiler (41), and later Klimont (76, 77, 78), verified Berthelot's conclusion by the isolation of oleodistearin from cacao butter, oleodistearin and oleodipalmitin from tallow, and stearodipalmitin from duck and goose fat. Hansen (53) and Kreis and Hafner (80) obtained palmitodistearin from mutton and beef tallow, and Bömer (16) and associates obtained dipalmitostearin and palmitodistearin from mutton tallow. From 1907 to 1938 Bömer and associates (17, 18, 19, 20, 21, 22) continued actively in the isolation of component glycerides from fats by fractional crystallization methods, investigating especially the composition of mutton tallow, lard, coconut oil, palm kernel fat, nutmeg butter, and babassu fat. From goose fat, Amberger and Bromig (4) separated palmitodistearin, stearodipalmitin, and stearodiolein.

All of these investigations gave support to the conclusion that fats and oils consist mainly of mixed triglycerides, but there was essentially no evidence relative to the configuration of the isolated products. Investigations since about 1927 by T. P. Hilditch (7, 62, 63, 64, 65, 66, 72) and associates, including progressive hydrogenation and oxidative researches, served to confirm and extend the view that fats are very complex mixtures of mixed triglycerides. In a few instances, the authors also assigned a definite configuration to the products isolated. Hilditch and Saletore, for example, reported the isolation of $\beta$-oleo-$\alpha,\alpha'$-distearin. The natural triglyceride upon oxidation gave a product which did not depress the melt-

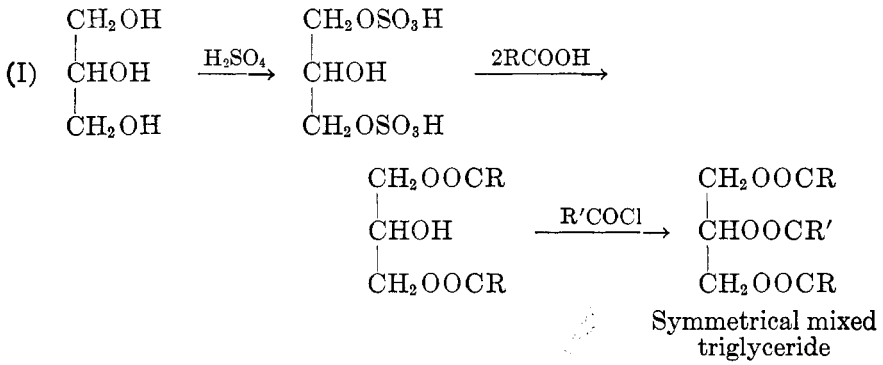
[2] We are indebted to The Buhl Foundation for grants in support of our work during the past three years, and to Professor G. Stegeman, Dr. T. H. Clarke, and Dr. H. E. Longenecker for their coöperation. The scope of our work has been accordingly extended to include the following: (*c*) thermal studies (specific heats and heats of combustion) of known synthetic isomers; (*d*) synthesis with unsaturated fatty acids; and (*e*) studies of the nutritional factors that markedly affect the composition of fats.

ing point of β-azelao-α,α′-distearin synthesized from α,α′-distearin. There was evidence, too, that the same symmetrical triglyceride could be found in a number of seed fats. Hilditch and Stainsby (71) obtained similar evidence that palmitodiolein, a constituent of many fats, had the beta or symmetrical configuration. Their conclusions were supported by the additional fact that palmitodistearin, obtained by hydrogenation of the oleic acid esters, melted at a temperature close to that of the synthetic symmetrical triglyceride. Other evidence relative to the specific configuration of mixed triglycerides has been obtained by Hilditch and Paul (68), Hilditch and Lea (67), and Banks, Dean, and Hilditch (6).

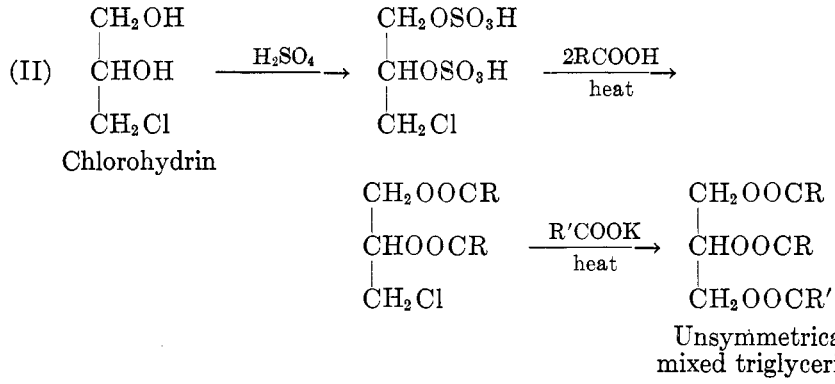
### III. DEVELOPMENT OF RELIABLE METHODS OF SYNTHESIS

Berthelot's (14) method of heating fatty acids with an excess of glycerol was perhaps the first laboratory procedure used for the synthesis of glycerides. By heating stearic acid with glycerol for a period of 20 hr. at 200°C. in a sealed tube, he obtained a monostearin and, by further heating, a distearin. Although the first two products were probably impure, he later obtained a synthetic tristearin corresponding to natural tristearin by heating monostearin with a large excess of stearic acid. Simple triglycerides were obtained by Garner (42) in almost theoretical yield by heating equivalent quantities of fatty acid and glycerol at 200°C. in an atmosphere of carbon dioxide. Although these and many other methods (57, 84, 97) are suitable for the preparation of simple triglycerides, they are of no practical value for the synthesis of pure mixed triglycerides.

The methods available for the preparation of mixed triglycerides before 1920 were chiefly those of Grün and associates (46, 48, 50). The preparation of a symmetrical mixed triglyceride by the action of an acyl chloride on glycerol disulfuric acid ester was carried out as indicated by the following procedure:

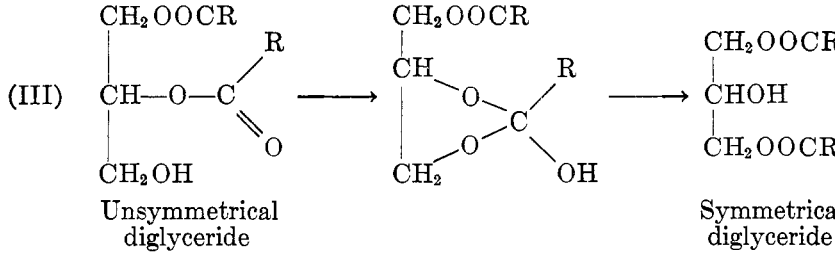


The supposed unsymmetrical triglyceride was prepared from the disulfuric ester of monochlorohydrin and the potassium salt of a fatty acid:




Grün and Limpächer (47) also employed the reaction methods of Romberg (87), Guth (52), and Kraft (79), using halohydrins with the sodium or potassium salts of the fatty acids, but discovered that glycide formation resulted in the production of other glycerides, diglyceryl esters, and unesterified fatty acids. Other investigators (5, 32) found that, because of (*a*) the temperature at which the reactions were carried out, (*b*) the uncertainties regarding the structure of the intermediate halohydrins and disulfuric esters used, and (*c*) the possibilities of rearrangement during the course of the reaction, the above methods were not satisfactory.

Fischer suggested that shifting of acyl groups might occur at high temperatures and then demonstrated that it actually occurred when he prepared mixed triglycerides by the methods of Grün. He postulated a mechanism to account for the rearrangement, based upon the production of a dioxolone derivative formed by the migration of a hydrogen atom on the carbon atom adjacent to the carbonyl group. The rearrangement, leading to the mistaken identification of $\beta$-monosubstituted and $\alpha,\beta$-disubstituted products, may be indicated as follows:




Hibbert and Grieg (59) reported the isolation of an intermediate dioxolone derivative in their attempts to prepare the monotrichloroacetate of

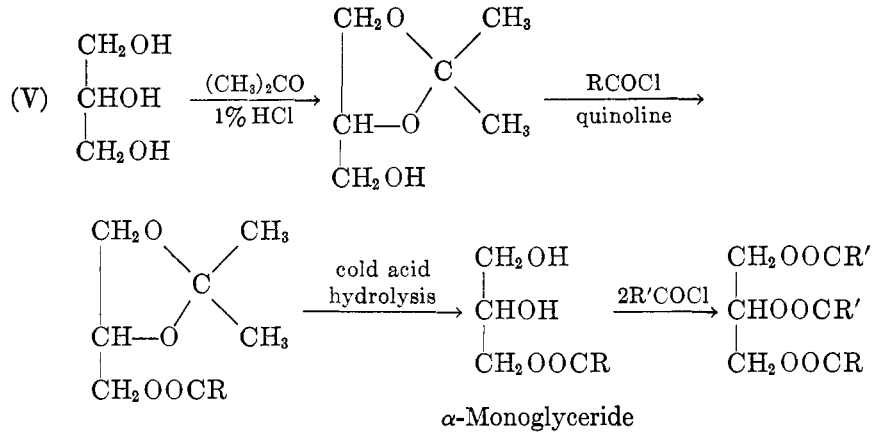
ethylene glycol. The tendency for the formation of a stable ring is apparently enhanced by increasing the polarity of the acyl group. Thus it is entirely plausible that the shifting of acyl groups from the beta to the alpha position may occur through the formation of a cyclic isomer.

The preparation of mixed triglycerides depends primarily upon (*a*) an initial selection of stable and pure starting compounds, (*b*) the preparation of pure mono- and di-substituted derivatives of glycerol, (*c*) the use of reaction conditions that do not cause unexpected shifts in position or replacement. The use of impure halohydrins as starting compounds and the above outlined (III) beta-to-alpha shifts of acyl groups have been frequent causes of error. Recognizing the need for intermediates of definite configuration, Fischer and associates (39, 40) developed methods for preparing $\alpha$-monoglycerides and symmetrical diglycerides and, from these intermediates, symmetrical and unsymmetrical mixed triglycerides. Alival, $\alpha$-iodohydrin, had been used for the preparation of supposed $\alpha,\beta$-diglycerides and thence unsymmetrical triglycerides, but Fischer succeeded in showing that the resulting diglyceride had undergone a beta-to-alpha shift:

$$\text{(IV)}\quad \begin{matrix}CH_2OH\\ |\\ CHOH\\ |\\ CH_2I\end{matrix} \xrightarrow{2RCOCl} \begin{matrix}CH_2OOCR\\ |\\ CHOOCR\\ |\\ CH_2I\end{matrix} \xrightarrow[\text{alcohol}]{AgNO_2 \text{ in hot aqueous}} \begin{matrix}CH_2OOCR\\ |\\ CHOH\\ |\\ CH_2OOCR\end{matrix} + AgI + HONO$$

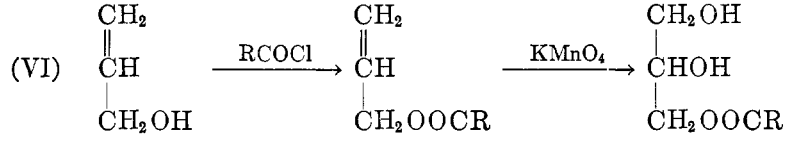
For the preparation of an $\alpha$-monoglyceride (V), glycerol was first condensed with acetone to give 1,2-isopropylideneglycerol (acetoneglycerol), the structure of which has been carefully verified by Hibbert and Carter (58). Irvine, McDonald, and Soutar (74) had shown previously that acetone in the presence of acid condenses with compounds containing vicinal hydroxyl groups. Their methylated 1,2-isopropylideneglycerol, prepared from the condensation product of acetone and glycerol, hydrolyzed to an alpha methyl ether identical with that obtained from allyl iodide. Hibbert and Carter were unable to obtain the 1,3-isopropylideneglycerol by direct condensation but did isolate it by alkaline hydrolysis of 2-benzoyl-1,3-isopropylideneglycerol. Fischer esterified 1,2-isopropylideneglycerol with an acyl chloride in the presence of cold quinoline and then removed the acetone by cold acid hydrolysis, giving an $\alpha$-monoglyc-

eride. The latter was then reësterified by a second acyl halide to yield the unsymmetrical triglyceride. The reactions were as follows:



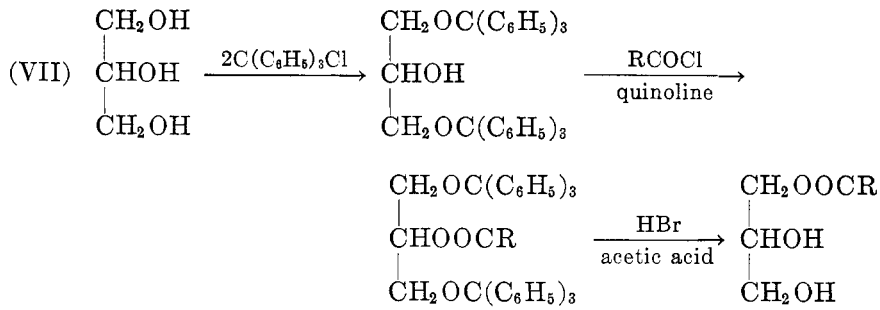

α-Monoglyceride

The structure of the monoglycerides prepared by this method was verified by Grün and Limpächer (47) by recondensation with acetone, and by Fairbourne and associates (33, 35) by the preparation of identical compounds, both from the allyl esters (VI) and by condensation with alpha monosodium glyceroxide (34, 37):




Abderhalden and Eichwald (1) contributed evidence to support the assigned structure by means of molecular rotation studies, and recently Hilditch (69) furnished additional evidence concerning the configuration on the basis of oxidation by lead tetraacetate. The synthesis of α-monoglycerides by the method of Fischer has repeatedly been found satisfactory by other investigators (3, 15, 26, 28, 83, 86, 95) for the preparation of unsymmetrical triglycerides.

Daubert and King (28) obtained good yields of pure α-monoglycerides also by the esterification of 1,2-benzylideneglycerol, followed by acid hydrolysis. The 1,2-isomer is frequently obtained as a predominant by-product when the 1,3-isomer is prepared for beta esterification. Jackson and King (75), studying the trityl ether methods discussed by Helferich and Sieber for preparing β-monoglycerides, found that, because of the shifting of acyl groups, α-monoglycerides were isolated:




These observations were verified by Verkade (98) in extensive studies of the use of trityl derivatives for the synthesis of glycerides.

Schuette and Hale (88) prepared $\alpha$-monoacetin and $\alpha$-monobutyrin by the direct esterification of glycerol in the presence of syrupy phosphoric acid. Robinson, Roche, and King (86) found that $\alpha$-monoacetin and $\alpha$-monobutyrin could not be obtained satisfactorily by hydrolysis of the esterified 1,2-isopropylideneglycerol. Young and Black (101) obtained $\alpha$-monolaurin by heating trilaurin with glycerol and trisodium phosphate under anhydrous conditions. Other direct esterification methods include those of Bellucci and associates (8, 9), Gianoli (43), and Hilditch and Rigg (69).

Fischer and Baer have recently developed an excellent method of preparing optically active 1,2-isopropylideneglycerol and thence the corresponding $\alpha$-monoglycerides (optically active) and mixed triglycerides (optically inactive), starting with the respective *d*- and *l*-mannitols. Since their work is treated in detail in another paper[3] in this Symposium, further reference to it will not be made here.

Relatively little work has been done with mixed triglycerides containing unsaturated acids. There is evidence, however, that a more comprehensive study of this field will be made in the near future, in part because the techniques of obtaining pure unsaturated acids have been greatly improved. Carter and Malkin (23) have reported physical data for a few unsaturated triglycerides and Amberger and Bromig (3), in 1922, prepared $\alpha$-monoölein from which a few monounsaturated unsymmetrical triglycerides were prepared. Recently, Black and Overley (15) reported the synthesis of $\alpha$-monolinolein from tetrabromostearoyl chloride and acetoneglycerol. The esterified acetoneglycerol was hydrolyzed in cold acid solution and then debrominated with zinc and alcohol to yield the unsaturated $\alpha$-monolinolein.

[3] Chem. Rev. **29**, 285 (1941).

A summary of the best published data for some of the triglycerides that have been isolated from natural products is given in table 1, together with

TABLE 1

*Synthetic and natural mixed triglycerides: a comparison of melting-point data for typical compounds*

| GLYCERIDE | MELTING POINT OF SYNTHETIC PRODUCT | ISOLATED NATURAL PRODUCTS* | | | | |
|---|---|---|---|---|---|---|
| | | Structure | Melting point | Author | Source | Year |
| | °C. | | °C. | | | |
| 1-Palmitodistearin | 64 | (unsym.) | 68.5 | Bömer | Lard | 1913 |
| 2-Palmitodistearin | 68 | (sym.) | 63.5 | Bömer | Goose fat | 1922 |
| | | (sym.) | 68.2 | Amberger | Cocoa fat | 1924 |
| | | | 63.5 | Kreis *et al.* | Tallow | 1903 |
| | | | 66.2 | Kreis *et al.* | Lard | 1903 |
| | | | 62.8 | Amberger | Hydrogenated butter fat | 1913 |
| | | | 63.6 | Bömer | Mutton tallow | 1909 |
| 1-Stearodipalmitin | 62.5 | (unsym.) | 57.5 | Amberger and Bromig | Goose fat | 1921 |
| 2-Stearodipalmitin | 68 | (sym.) | 63.0 | Amberger and Bromig | Goose fat | 1921 |
| | | | 57.5 | Bömer | Mutton tallow | 1909 |
| | | | 58.2 | Bömer | Lard | 1913 |
| | | | .55 | Hansen | Beef tallow | 1902 |
| | | | 58 | Amberger | Butterfat | 1913 |
| | | | 59 | Keimont | Goose fat | 1909 |
| 1-Palmitodimyristin | 54 | | 45.2 | Bömer | Palm kernel oil | 1924 |
| 2-Palmitodimyristin | 60 | | 45.1 | Bömer | Coconut oil | 1920 |
| 1-Myristodilaurin | 43 | | 34.9 | Bömer and Hüttig | Babassu fat | 1938 |
| 2-Myristodilaurin | 50 | | 33 | Bömer | Coconut oil | 1920 |
| | | | 33 | Bömer | Palm kernel oil | 1924 |

* Specific structure not assigned unless indicated.

comparable data based on synthetic glycerides of known structure. Perhaps the need for reliable reference data based upon synthetic products of

known constitution will be indicated by the record. Bömer, Amberger, Klimont, and their collaborators are generally credited with having done the most thorough work that has been published relative to the separation of individual triglycerides from natural fats.

A number of mixed glycerides containing oleic and palmitic, oleic and stearic, or oleic, palmitic, and stearic acids have been isolated, but the recorded data are very inconsistent. Now that pure unsaturated fatty acids are becoming available for making intermediates, there is evident need for synthetic work with such series, in even greater degree than for the saturated series.

The data gained from the study of synthetic glycerides in recent years have been reasonably consistent in their indication that the symmetrical mixed triglycerides, compared to the unsymmetrical isomers, are less soluble, have higher melting points, and have higher indices of refraction. There is also some evidence that the symmetrical types are more common in occurrence (reference 23, page 181 *et seq.*), though a part of the evidence may be the result of their lesser solubility. Only a small amount of work has been accomplished relative to the synthesis of isomeric glycerides containing three fatty acids.

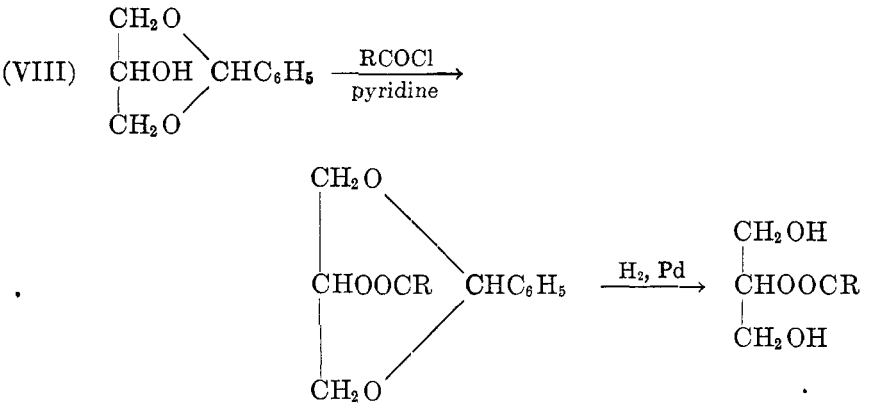
## IV. MONOGLYCERIDES OF THE BETA TYPE

Many studies have also been directed toward finding suitable methods of preparing the $\beta$-monoglycerides and the $\alpha,\beta$-diglycerides. Grün (50) supposedly prepared a beta ester of glycerol by treating 1,3-dichlorohydrin with an acyl chloride and subsequently removing the chlorine atoms. He also prepared what he believed to be $\beta$-monolaurin from $\beta$-monochlorohydrin and the potassium soap of the fatty acid. Both of these reactions have been investigated by Fairbourne (34, 35) and have been found to be of little value for the preparation of $\beta$-monoglycerides. Grün originally differentiated the isomeric monoglycerides by reaction with phenylurethan, but Fairbourne proved that the $\alpha$- and $\beta$-monolaurins prepared by Grün's method gave identical diphenylurethans. Furthermore, he found that the $\beta$-monochlorohydrins used by Grün were mixtures of $\alpha$- and $\beta$-isomers. Hibbert, Whelen, and Carter (61) contributed a valuable reference compound for identifying glycerides by preparing the beta methyl ether of glycerol and differentiating it from the alpha monomethyl ether obtained by Irvine, McDonald, and Soutar (74). They, as well as Fairbourne (31, 36), found no evidence to indicate a shift of methoxyl groups under common conditions of reaction, but Gilchrist and Purves (44) reported finding evidence of migration (unconfirmed). Helferich and Sieber (55, 56) undoubtedly obtained true beta aromatic esters of glycerol. Acid hydrolysis of 2-benzoyl-1,3-ditritylglycerol and 2-*p*-nitro-

benzoyl-1,3-ditritylglycerol, prepared from 1,3-ditritylglycerol, yielded the β-monobenzoate and β-*p*-nitrobenzoate. Although they prepared the analogous aliphatic beta esters of ditritylglycerol, they did not succeed in preparing the derived simple fatty acid esters of glycerol. Jackson and King (75) prepared the β-palmityl- and β-stearyl-ditritylglycerols and found that acid hydrolysis, even at 0°C., gave good yields of the rearranged α-monopalmitin and α-monostearin. In fact, the method is one of the best for preparing pure α-monoglycerides.

Bergmann and Carter (12) first prepared a true β-monoglyceride of a fatty acid. Their method was based upon the catalytic reduction by means of hydrogen and palladium, in neutral solution and under pressure, of an esterified 1,3-benzylideneglycerol (VIII). Fischer (38), as early as 1894, had studied the products resulting from the condensation of benzaldehyde and glycerol, and later the same reaction had been investigated by Irvine, McDonald, and Soutar (74). Hibbert and Carter (58) succeeded in separating the two possible isomers by differences in solubility and identified the structures by methylation and hydrolysis.

Bergmann and Carter prepared β-monoacetin, β-monopalmitin, and glycerol β-monobenzoate by catalytic reduction of the corresponding beta esters of 1,3-benzylideneglycerol according to the following reactions:



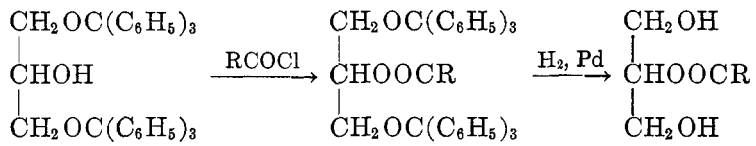
Stimmel and King (89) studied the method and the stability of the resulting esters further, including the preparation of the β-monoglycerides of capric, lauric, myristic, and stearic acids. Although the melting point of each of the beta esters was lower than that of the unsymmetrical isomer, the melted beta esters did not undergo rearrangement rapidly except when the reaction was catalyzed by hydrogen or hydroxyl ions. The beta esters were more soluble in organic solvents than the respective isomeric α-monoglycerides, in contrast to the lesser solubility of the symmetrical mixed

triglycerides and the aromatic acid glycerol esters of the beta type. Proof of structure of the $\beta$-monomyristin was obtained by converting it to the known 2-myristyl-1,3-distearin (86) by treating the beta ester with two moles of stearyl chloride under controlled conditions.

Hibbert and Carter (58), in testing the preparation of aromatic beta esters by hydrolysis of the esterified 1,3-benzylideneglycerols with $N/40$ hydrochloric acid at 80°C., observed a rearrangement to the corresponding $\alpha$-isomers. King and associates (28, 89), in studies of the effects of acid and base catalysis, observed that $\beta$-monopalmitin shifted completely to the $\alpha$-isomer on standing for 24 hr. in an alcoholic solution of $N/20$ hydrochloric acid or $N/10$ ammonia, and that the $\beta$-*p*-bromobenzoate of glycerol shifted to the $\alpha$-isomer under similar conditions when catalyzed by $N/10$ hydrochloric acid or $N/10$ ammonia. Their observations demonstrated a distinctly greater stability for aromatic monoglycerides and for unsymmetrical diglycerides of the 1,2 type, in agreement with the observations underlying Fischer's early work.

A method suggested by Verkade and associates (94) for the preparation of aliphatic $\beta$-monoglycerides was accomplished experimentally by Daubert (17). It involved the catalytic detritylation of the esterified 1,3-ditrityl ether of glycerol, and the reactions were as follows:

(IX)




As mentioned previously, acid hydrolysis for the removal of the trityl groups could not be used for the preparation of aliphatic $\beta$-monoglycerides because of acyl migration. The above reduction method (IX) and that of Bergmann and Carter (VIII) provide two very satisfactory methods for preparing $\beta$-monoglycerides, because good yields of the intermediates can be obtained as highly purified products, and the final steps also give good yields of pure products.

## V. PREPARATION OF UNSYMMETRICAL DIGLYCERIDES

In the preparation of diglycerides, the unsymmetrical aliphatic type has offered the most serious difficulty. Grün (48) reported the preparation of symmetrical dimyristin by heating glycerol disulfate with myristic acid dissolved in sulfuric acid, and the unsymmetrical dimyristin by heating the disulfate of $\alpha$-monochlorohydrin with the fatty acid and subsequently removing the chlorine with silver nitrate. Fairbourne, using Grün's methods, succeeded only in the isolation of the symmetrical diglyceride.

Other investigations (49, 90) have also indicated the unstable character of beta aliphatic groups under such conditions of reaction. Guth (52), and later Renshaw (85), prepared an ester which they thought to be 1,2-distearin, but each probably obtained the symmetrical isomer or a mixture. Heiduschka and Schuster (54) reported the preparation of unsymmetrical dipalmitin and distearin by the methods of Guth, and supposedly proved the configuration of these esters by reaction with thionyl chloride. Fairbourne, however, found that their assumption that thionyl chloride reacts only with primary hydroxyl groups was without foundation, and further, that the unsymmetrical diglycerides isolated by them were probably the symmetrical diglycerides or a mixture of the two isomers. Whitby (100) had apparently prepared 2-palmityl-1,3-distearin from 2-palmityl-1,3-dichlorohydrin by heating the latter with two moles of silver stearate. Thomsen (91) later reported the preparation of 1,2- and 1,3-dimargarins by a method similar to Whitby's, but Fairbourne proved that both isomers melted at the same temperature when purified. Delaby and Dubois (30) reported the preparation of the 1,2- and 1,3-diformates of glycerol by direct esterification, but this method, as well as the methods of Humnicki and Lunkiewiscz (73) and Weismann and Haskelburg (99) (for the preparation of diglycerides) apparently involved unrecognized shifting of acyl groups. The preparation of diglycerides has also been reported by Abderhalden and Eichwald (2) and Bergmann (10, 11), using indirect methods with propylamines. Although they obtained evidence of the presence of an unsymmetrical isomer by rotation studies, their products apparently were not pure. While many of the methods (48, 49, 54, 85, 91, 100), including those of Grün and Slepnick (51), in which fatty acid soaps reacted with symmetrical dichlorohydrins and 1-chloro-3-acylglycerol, have been used and may be satisfactory for the preparation of symmetrical diglycerides, they are of no value for the preparation of the unsymmetrical isomers. In several instances it appears that impure halohydrins were used.

A widely used method for preparing symmetrical diglycerides is that of Fischer, Bergmann, and Bärwind (40), using $\alpha$-iodohydrin (alival), as outlined previously (IV). The investigations of trityl ether reactions (75, 96) have provided an excellent method for the preparation of symmetrical aliphatic diglycerides. Since alival is no longer readily available, and its use involved difficulty in purifying the reaction products, the trityl intermediates may well replace the use of alival. After hydrolysis of the 1-trityl-2,3-diacylglycerols with hydrogen bromide in chloroform, the symmetrical, rather than the unsymmetrical, diglycerides were isolated regularly and with good yields of pure products (X):

(X) $CH_2OC(C_6H_5)_3$ | $CHOH$ | $CH_2OH$ $\xrightarrow{2RCOCl}$ $CH_2OC(C_6H_5)_3$ | $CHOOCR$ | $CH_2OOCR$ $\xrightarrow{HBr}$ $CH_2OOCR$ | $CHOH$ | $CH_2OOCR$

In contrast, Helferich and Sieber (55, 56) were successful in the preparation of aromatic unsymmetrical diglycerides by hydrolytic detritylation of the esterified alpha monotrityl ethers of glycerol.

Golendeev (45) reported the preparation of unsymmetrical diglycerides from allyl esters according to the following reactions:

(XI) $CH_2$ ‖ $CH$ | $CH_2OCOR$ $\xrightarrow{HOI}$ $CH_2OH$ | $CHI$ | $CH_2OOCR$ $\xrightarrow[heat]{RCOOK}$ $CH_2OH$ | $CHOOCR$ | $CH_2OOCR$

Although this method has not been fully investigated, it is very improbable that the reactions could be completed without a partial or complete beta-to-alpha shift.

The catalytic detritylation of a 1,2-diacyl-3-tritylglycerol by hydrogen gas in neutral solution, suggested in a paper by Verkade and associates (93), was used successfully by Daubert and King (29). It is apparently the first satisfactory method reported for the preparation of unsymmetrical aliphatic diglycerides. Daubert and King have also reported a new and satisfactory method of preparing 1,2-diglycerides of fatty acids, involving catalytic reduction of esterified 1-glyceryl benzyl carbonate (XII) (29). The latter was prepared with good yields from alpha monosodium glyceroxide and benzyl chloroformate. The resulting 1,2-diglycerides were identical with those prepared by reduction of the esterified alpha trityl ethers. The reactions were as follows:

(XII) $CH_2ONa$ | $CHOH$ | $CH_2OH$ + $COCl$ | $CH_2$ | $C_6H_5$ $\longrightarrow$ $CH_2OOCOCH_2C_6H_5$ | $CHOH$ | $CH_2OH$ $\xrightarrow{2RCOCl}$ $CHOOCOCH_2C_6H_5$ | $CHOOCR$ | $CH_2OOCR$ $\xrightarrow{H_2, Pd}$ $CH_2OH$ | $CHOOCR$ | $CH_2OOCR$

Because of the unrecognized tendency of acyl groups to migrate and the use of intermediates of uncertain constitution, the methods of Guth and many other investigators (46, 48, 50, 52, 79, 87) for the preparation of

mixed triglycerides containing two fatty acids led to the publication of a large amount of conflicting data for many of the synthetic glycerides. Although the preparation of triglycerides from unsymmetrical diglycerides of definite configuration has been accomplished, the method is obviously hazardous (29) because of the risk of acyl migration. Both $\beta$-monoglycerides and symmetrical diglycerides are available for the synthesis and verification of structure of symmetrical mixed triglycerides.

### VI. RECENT PHYSICOCHEMICAL STUDIES OF ISOMERIC GLYCERIDES

Malkin and associates (21, 23, 82) have made a detailed thermal and x-ray pattern study of many synthetic mixed triglycerides as well as of the $\alpha$-monoglycerides and 1,3-diglycerides used as intermediates. They have found that differences in melting and transition points and x-ray data serve to distinguish clearly between the isomeric pairs (*cf.* Ferguson and Lutton[4]).

Clarke and Stegeman (25) have made careful measurements of the specific heats and heats of combustion of the isomeric $\alpha$- and $\beta$-monopalmitins. Their data provide good thermodynamic evidence of the greater stability of the $\alpha$-forms: "The heats of combustion of alpha- and beta-monopalmitin reduced to the standard state, $-\Delta U_R$, are reported as 2778.78 $\pm$ 0.36 and 2788.30 $\pm$ 0.67 kcal. per mole for the reaction carried out at one atmosphere pressure and 25°. The difference in the heats of formation or the heat of the shift of the beta form to the alpha form of $-9.52$ kcal. per mole is in agreement with the chemical behavior of the isomers but is larger in magnitude than had been expected." Judging from their known resemblance in properties, it is likely that isomeric symmetrical and unsymmetrical diglycerides would show similar differences in energy values, but the data for such pairs are not yet available.

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