The Chemical Synthesis of Glycerides

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NUMEROUS industrial uses of glycerides have resulted directly from the laboratory preparation of glycerides of known configuration which, with their intermediates, were synthesized to elucidate the structure of natural fats too complex to be resolved into their simpler components by analytical means. These syntheses presented many individual problems since each usually involved the preparation, in pure form, of only one of several isomers. Consequently, the large number of desired compounds and the specific techniques necessary for their synthesis has resulted in a very extensive literature which although partially summarized in some treatises and older reviews is not readily available. It seems desirable, therefore, to present a brief systematic review of the methods of synthesis of the various glycerides with emphasis on the more recent developments and their application.

The chemical synthesis of glycerides is essentially a process of partial or complete esterification of organic aliphatic acids and glycerol, resulting in mono-, di-, or triglycerides depending upon whether one, two, or three of the hydroxyl groups of glycerol are esterified. The process may vary in complexity from that of a simple direct esterification yielding a homogeneous triglyceride to a complex series of reactions yielding a triglyceride containing three different fatty acids in predetermined positions.

The increasing complexity of synthesis is evident if the number of isomeric forms of glycerides is considered. Thus, a monoglyceride may be of the "alpha" or "beta" type, depending upon whether one of the terminal hydroxyls or the central hydroxyl group of the glycerol molecule is esterified. Similarly, a diglyceride containing only one fatty acid type may be of the symmetrical (1,3-) or unsymmetrical (1,2-) type. If two fatty acids are involved, three isomers are possible:

CH_2OCOR^1	CH_2OCOR^2	CH_2OCOR^1
$CH\text{-}OCOR^2$	$CH\text{-}OCOR^1$	$CH\text{-}OH$
CH_2OH	CH_2OH	CH_2OCOR^2

Finally, triglycerides may be of six types, depending upon the number and position of the acids involved:

CH_2OCOR	CH_2OCOR	CH_2OCOR^1
$CH\text{-}OCOR$	$CH\text{-}OCOR^1$	$CH\text{-}OCOR$
CH_2OCOR	CH_2OCOR^1	CH_2OCOR^1

Isomerism of other types may also be present: (1) that due to the presence of an optically active acid, (2) that due to the asymmetry on the central carbon atom of glycerol, giving the possibility of optically active glycerides, and (3) isomerism of the fatty acids themselves, i.e., linolenic and eleostearic, oleic and elaidic, etc.

For the purposes of this review, specific syntheses of mono-, di-, and triglycerides are taken up first. This is followed by a discussion of general syntheses and applications.

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Synthesis of Monoglycerides

Berthelot's (1) classical method for the preparation of monoglycerides involved heating fatty acids with an excess of glycerol in a sealed tube. The very impure product secured led Romberg (2), Guth (3), and Kraft (4) to attempt the synthesis by heating equivalent quantities of monochlorhydrin (or monobromhydrin) with the finely divided sodium salt of the fatty acid. Grün employed this method and later discovered (5) that glycide formation occurred as a side reaction, resulting in the production of other glycerides, diglycerol esters, and considerable unesterified fatty acid. Potassium salts were found to be more satisfactory. However, uncertainties in the structure of the chlorhydrins as well as rearrangements which occurred at the high temperatures employed seriously limited the usefulness of this method (6, 7). Specimens of so-called beta monoglycerides obtained either by the soap reaction described above, or by the action of an acyl halide on the 1,3-dichlorhydrin followed by hydrolysis of the chlorine residues (8, 9, 10), have been shown to be really alpha monoglycerides in varying degrees of purity (11, 12, 13).

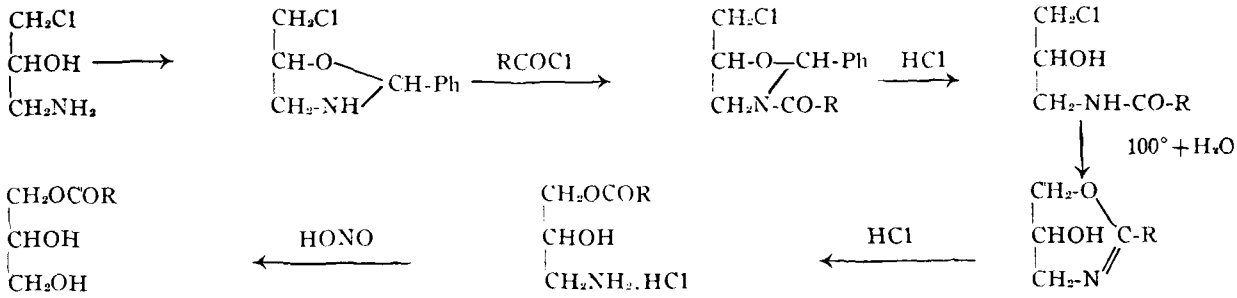
In 1920 Fischer (14) showed that in the presence of pyridine or quinoline, acyl halides reacted in the cold with the free hydroxyl group in acetone glycerol (1,2-isopropylidene glycerol) giving a product which on cold acid hydrolysis of the acetone group yielded monoglycerides with the fatty acid present only in the alpha position. The 1,2-isopropylidene glycerol was prepared by condensing dry acetone and glycerol in the presence of 1% HCl. The structure of this intermediate was indicated from the work of Irvine, MacDonald, and Soutar (15) who had previously shown that in the presence of acid acetone condensed with compounds containing hydroxyl groups on adjacent carbon atoms, and from the fact that the methylated product of 1,2-isopropylidene glycerol was found on hydrolysis to be identical with the alpha methyl ether of glycerol prepared from allyl iodide. The structure of the monoglycerides has been confirmed by acetonization (16) and by lead tetraacetate oxidation (17), as well as by numerous other indirect methods. Various laboratories have repeated the synthesis (6, 18, 19, 20, 21, etc.).

CH_2OCOR^1	CH_2OCOR^2	CH_2OCOR^2
$CH\text{-}OCOR^2$	$CH\text{-}OCOR^1$	$CH\text{-}OCOR^3$
CH_2OCOR^3	CH_2OCOR^3	CH_2OCOR^1

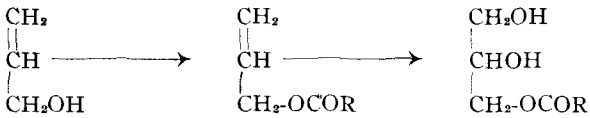
Recently, optically active acetone glycerol has been used in the preparation of optically active monoglycerides (22, 23, 24, 25, 26). Dextro- or laevo-mannitol was acetonated to the corresponding 1,2,5,6-diacetone mannitol which was cleaved by lead tetraacetate into two moles of optically active acetone glyceraldehyde. Subsequent reduction of the aldehyde yielded the active acetone glycerol from which the monoglycerides were prepared in the usual way.

Bergmann (27) has prepared monoglycerides in an indirect manner by treating epichloramine with ben-

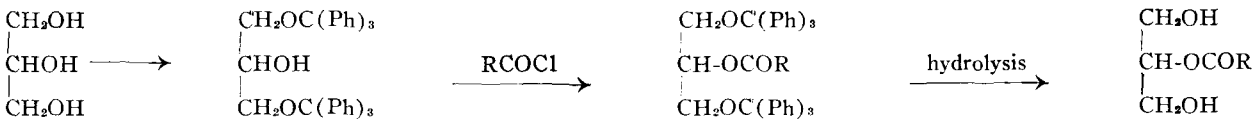
zaldehyde to form 2-phenyl-5-chloromethyloxazolidine which forms an acyl derivative by reaction with an acid chloride in chloroform solution. Dilute HCl hydrolyzes this to the 1-acyl-3-amino glycerol hydrochloride from which, by the action of nitrous acid, the alpha monoglyceride is obtained. The reactions involved are represented below:



Fairbourne (28, 12) prepared alpha monoglycerides by making allyl esters which were subsequently oxidized, using permanganate in acetone, to the alpha monoglycerides.

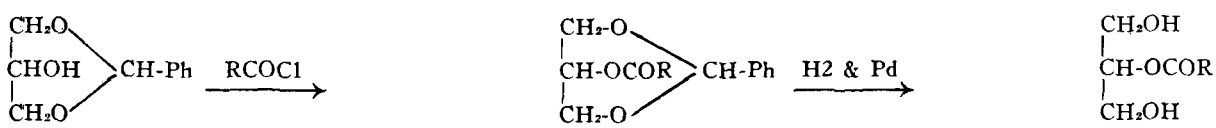


The preparation of the 1-monotrityl ether and the 1,3-ditrityl ether of glycerol by Helferich et al. (18) made available an entirely new method of glyceride synthesis of wide applicability. Using the 1,3-ditrityl ether of glycerol, for example, aromatic beta monoglycerides were prepared by acylation followed by hydrolysis of the trityl groups (29, 30).



The method as such is not suitable for the preparation of aliphatic beta monoglycerides because acyl migration occurs during the hydrolysis of the trityl group (31). This may be avoided if the trityl groups are removed by reduction (32).

The first preparation of a true beta monoglyceride of a fatty acid was reported by Bergmann and Carter (33). Benzaldehyde and glycerol were condensed to 1,2- and 1,3-benzylidene glycerol, which were separated by solubility differences. Acylation of the 1,3-benzylidene glycerol and subsequent reduction of the benzylidene residue produced pure beta monoglycerides.



Stimmel and King (34) have repeated the method. Hydrolysis of the benzylidine group allows acyl migration with the production of alpha monoglycerides (35).

The direct esterification of glycerol (1, 36, 37, 38) has served as a convenient method for the preparation of monoglycerides, with certain limitations (39). In general, fatty acids are heated with about 10 times their weight of glycerol at 170-180°, the yields being increased by the removal of water formed as a by-product and by the presence of catalysts. The removal of water is usually effected by the use of vacuum or by a stream of inert gas passed through the reaction mixture. Schuette and Hale (40) prepared alpha monoacetin and alpha monobutyrin by direct esterification of glycerol in the presence of sirupy phosphoric acid. The use of soaps of Al, Mg, Sn, and Zn has been patented (41), as also the use of alkali glycerates (42). Hilditch has shown (17) that yields of monoglycerides are increased by employing a medium in which both the alcohol and the acid are freely soluble. Thus, using a weight of phenol equal to the weight of fatty acids, yields of monoglycerides up to 90% have been reported, depending upon the temperature, time of reaction, and ratio of glycerol to acid. Beta naphthylene sulfonic acid increases the yield of total esters but somewhat decreases the amount of monoglycerides. The preparation of pure alpha monolaurin and monopalmitin using this method has been reported. The process is now patented (43).

Technically, monoglycerides are usually produced by heating glycerol with fats at 180-250° in the presence of catalysts (44, 45). Di- and triglycerides are also among the products, but their amounts may be considerably reduced by careful attention to experimental conditions. For kernel fats of average molecular weight equal to 850, Schönfeld (46) suggested using 6-8% of their weight in glycerine for diglycerides, and 12-15% for monoglycerides. With these quantities, temperatures under 180° (with high vacuum) are suitable for monoglycerides, and 180-250° for diglycerides. Temperatures higher than 250° or too prolonged heating result in the production of triglycerides. Alkali alcoholates and soaps are commonly used catalysts for direct esterification (47, 48, 49, 50, 51). Recently, monolaurin was prepared by heating equal weights of trilaurin and glycerol under nitrogen for 15 minutes in the presence of a small amount of trisodium phosphate (52). The reverse reaction occurred at high temperatures.

Synthesis of Diglycerides

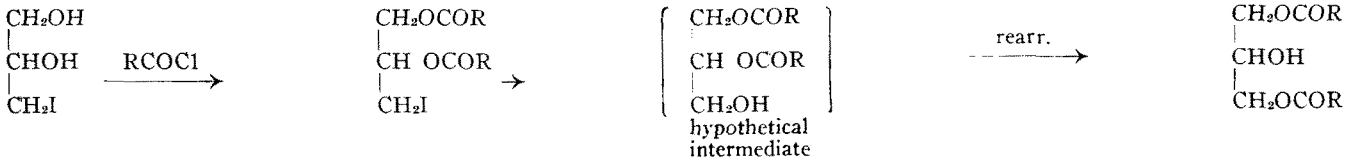
Grün prepared symmetrical diglycerides by heating glycerol disulfate with a fatty acid dissolved in concentrated sulfuric acid (53). Unsymmetrical diglycerides were prepared by making the disulfate of alpha mono-

chlorhydrin, heating with a fatty acid, and then removing the chlorine by means of silver nitrite (54). Either method, however, resulted in the production of symmetrical diglycerides owing to the instability of beta aliphatic acyl groups in the presence of acid (12, 13, 55). The migration of acyl groups from the beta to the alpha positon was also responsible for the failure of Grün's unsymmetrical diglyceride preparations (10) made by the acylation of alpha monochlorhydrin and subsequent removal of the chlorine atom by hydrolysis.

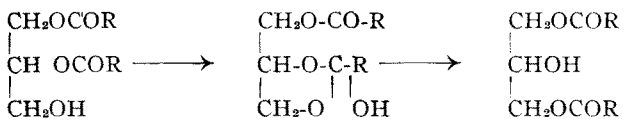
Diglycerides have also been prepared by the reaction of fatty acid soaps with symmetrical dichlorhydrins or 1-chloro-3-acyl glycerols (8, 17, 56, 57). Unsymmetrical dichlor- or dibromhydrins (58) yield symmetrical diglycerides owing to acyl migration.

Bergmann (59, 27) prepared unsymmetrical aromatic diglycerides in an indirect way by condensing 1-amino glycerol or 1-chloro-3-amino glycerol with benzaldehyde, thus permitting stepwise acylation. The fact that slight optical activity was noted in the compounds produced indicates an unsymmetrical structure for them, although their purity is questionable.

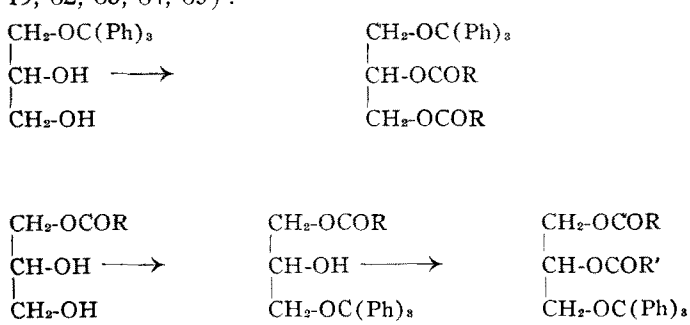
Perhaps the most convenient method for preparing symmetrical diglycerides is the alival method of Fischer (60), later improved by King et. al. (6). Alpha iodohydrin ('alival") is treated with an acyl halide to form a diester. The iodine is then removed by refluxing with alcoholic silver nitrite, the unsymmetrical compound first produced rearranging immediately to the stable symmetrical form.



The shift from the beta to the alpha configuration was indicated by the fact that the triglyceride prepared by introducing a new acid containing a different hydrocarbon chain (R') into the diglyceride prepared from alival was not identical with the triglyceride prepared from an alpha monoglyceride containing the hydrocarbon chain R' on acylation with RCOCl, as would be the case had migration not occurred. Fischer explained the shift on the basis of an inner ring formation, later substantiated by the isolation of similar cyclic compounds when the R group was strongly negative (61).

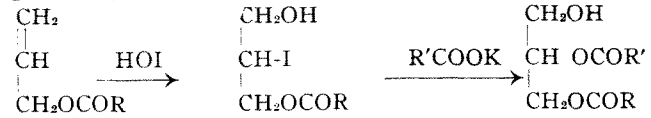


Diglyceride synthesis by means of trityl ethers of glycerol is illustrated in the following equations (29, 30, 19, 62, 63, 64, 65):



It is apparent that the proper use of the trityl ethers permits the synthesis of monoacid or diacid symmetrical or unsymmetrical diglycerides. However, the details of the reduction of the trityl group have not yet been published.

The preparation of unsymmetrical diglycerides from allyl esters by the addition of hypoiodous acid and subsequent reaction with a potassium soap has been reported by Golendeev (66).

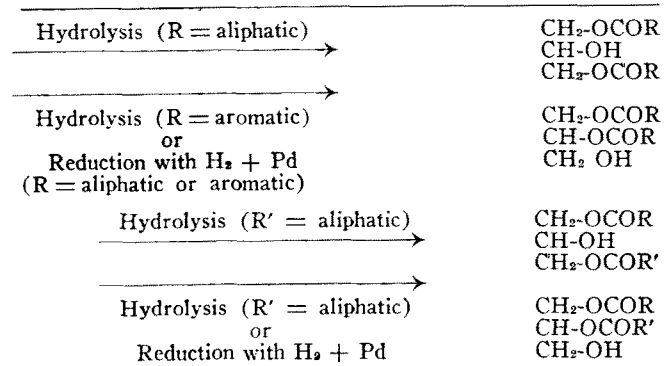


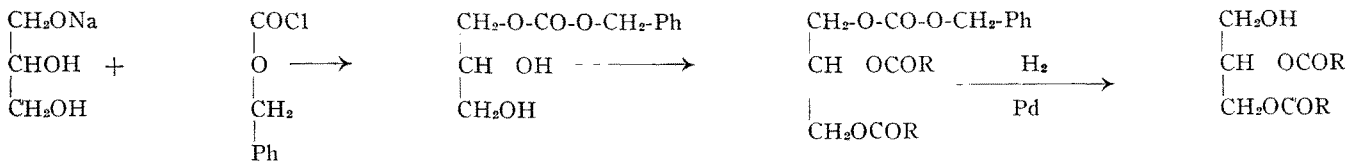
The possibility of acyl migration is not precluded, however.

Recently, Daubert and King (67) have published a new synthesis of unsymmetrical diglycerides. In this method the alpha hydroxyl group of glycerol is blocked by treating alpha monosodium glyceroxide with benzyl chloroformate to produce 1-glyceryl benzylcarbonate. The two free hydroxyl groups are then acylated using an acyl halide in quinoline at room temperature, and the diglyceride formed by catalytic reduction.

In this connection, Daubert and King (55) made a quantitative study of acyl migration and found that 0.1N HCl or NH_4OH in alcoholic solution caused both aromatic and aliphatic monoglycerides to undergo a complete shift from the beta to the alpha position in a short time at room temperature. In more dilute acid or alkali a marked contrast between aromatic and aliphatic beta esters was evident: N/150 HCl and N/80 NH_4OH were about as effective upon an aliphatic ester as N/20 HCl or N/15 NH_4OH were upon an aromatic ester. Neither aliphatic nor aromatic beta esters exhibited a shift to the beta isomer when held at seven degrees above their melting points for one hour in the dry state. Aromatic unsymmetrical diglycerides were stable to 0.1N HCl or NH_4OH at room temperature, but aliphatic unsymmetrical diglycerides exhibited considerable acyl migration under these conditions (68).

Like monoglycerides, diglycerides may be prepared commercially by direct esterification or by ester exchange, using fats and glycerol (see under monoglycerides). A recent preparation of diglycerides was carried out by heating linseed and cottonseed oils for 15 minutes at 280° with a slight excess of glycerol, with constant stirring, in the presence of 0.1% lead oxide (69).





Synthesis of Triglycerides

Triglycerides may be prepared by the action of a fatty acid anhydride or, more commonly, a fatty acid chloride on mono- or diglycerides (53, 54, 8, 60, 18, 57, 70, 71, 19, 72). Averill, Roche and King (6) successfully treated mono- or diglycerides with a slight excess of an acyl halide dissolved in quinoline or pyridine. Recently, tricaprylin has been prepared directly from glycerol (73) using aqueous potassium hydroxide to take up the HCl formed in the reaction. High yields of tributyrin have been reported from the reaction of glycerol with sodium propionate in the presence of PCl_5 (74), and various monoacid triglycerides have been prepared by heating symmetrical tribromopropane with the lead salts of fatty acids (75).

The direct esterification of glycerol is the method used commercially for the synthesis of triglycerides. although few are prepared commercially, the principal exceptions being Synourin and Intarvin. Berthelot's classical synthesis (1) was improved by heating under diminished pressure (36), and in 1928 Garner (76) prepared simple triglycerides in almost theoretical yield by heating equivalent quantities of fatty acid and glycerol for 6 hours at a temperature of 200° in an atmosphere of CO_2. Verkade (77) obtained an 82% yield of tristridecylin by heating glycerol with a slight excess of the acid under reduced pressure and in an atmosphere of carbon dioxide. Zinc dust was used as a catalyst. Recently, the preparation of triglycerides of unsaturated fatty acids by direct esterification was accomplished by Wheeler, Riemenschneider and Sando (146). Other preparations are patented (78, 79). In general, catalysts, high temperature, and low ratio of glycerol to fatty acid favor the production of increasing amounts of triglycerides. Catalysts include Cd, Sn, Zn, Mg, Th, Al, Ti [usually as salts or oxides], metallic alloys, Twitchell reagent and alkali metal soaps. carbonates, and acoholates (44, 80).

General Synthesis of Glycerides

The direct esterification of fatty acids (36, 37, 38) while not usually resulting in the production of homogeneous products of definite configuration, is of considerable technical importance. For example, the drying time of oils may be decreased by esterifying any free fatty acid present, using calcium soaps as catalysts (81). Glycerides of higher fatty acids have been made by directing, at a high temperature, the acid and alcohol in the liquid phase on to filling materials in a tower, if necessary, in the presence of a catalyst (82). Coke may be used as a filling material and reduced pressure employed (83). Sometimes the component of lower boiling point is introduced in vapor or mist form, and under diminished pressure, into the liquid higher boiling component. The temperature is maintained above the boiling point of the lower boiling component, and a carrier gas such as nitrogen, water vapor, or hydrogen (for simultaneous hydrogenation) may be employed. Catalysts include magnesium oleate, phosphoric acid, or zinc chloride (84, 85). The use of the Twitchell reagent is described (86). Unsaturated or hydroxy acids have been esterified directly (87, 88), and non-drying sirupy products soluble in organic solvents are obtained by esterifying high molecular weight hydroxy acid glycerides with phthalic acid, phthalic anhydride, adipic acid, or other saturated acids (89). Mixed esters of glycerol with aliphatic acids and phosphoric acid prepared in a similar manner are of therapeutic value (90) and phenylaliphatic glycerides (91) may be used in the production of phenyl ethyl alcohol.

Glycerides produced by the hydrolysis of fats are of great practical importance. Grün (92, 93) reported the preparation of mono- and diglycerides by the acid hydrolysis of triglycerides. However, the usual procedure is to heat fats with glycerol thus esterifying the glycerol at the expense of fatty acids from the fat (94, 95, 96, 97, 98, 99). In this way glycerides are prepared which may be used as such or as raw material for the production of mixed glycerides containing acids of drying oils or rosin acids (94). The preparation of fatty acid esters containing unesterified hydroxyl groups is effected by heating the triglyceride (fat) with a polyhydric alcohol in the presence of a catalyst such as a soap of a metal of valence not greater than two. The soap may be formed *in situ* by partial saponification of the fat with an alkaline compound, e. g., Na_3PO_4, Na_2CO_3, $NaHCO_3$, or NaOH (97). Edible esters from cottonseed oil and glycerol have been prepared by heating five parts of the oil with one part of glycerol and about 0.1-0.2% of concentrated sulfuric acid (99).

Glycerol esters of amino acids have been prepared by the action of chlorhydrins on the sodium salts of the acids (100, 101, 102, 103, 104). Esters of salicylic acid have also been prepared (105, 106, 107, 108), and an oil readily absorbed by the skin is claimed by the esterification of peanut oil with salicylic acid at 200-220° under a carbon dioxide pressure of two atmospheres (107). In the presence of sulfuric acid unsaturated higher aliphatic acids or their glycerol esters may be condensed with phenols to varying degrees. The lower condensation products are said to be easily sulfonated and yield sulfonic acids which may be used as auxiliary treating agents in the textile industry (109). Glycerol esters of rosin are prepared by heating the components in a current of air to 275-280° in the presence of catalysts such as Zn, Mg, Al, Cd, or sodium acetate, and have properties similar to rosin (110). The preparation of glycerides containing silicon has been described (111, 112) and attempts to prepare ring glycerides by the direct esterification of dicarboxylic acids have been reported (113). Also, "alkyd resins," produced by the reaction of glycerol with polybasic organic acids, may be modified with various fatty acids or oils to give many different type products of commercial importance (114, 115).

Synthetic fats and soaps may now be produced from the fatty acids obtained by the controlled oxidation of hydrocarbons obtained from coal (116) or petroleum (117). It is reported (118) that Germany is expected to increase production of synthetic fatty acids from paraffin to 40,000 tons yearly because of the scarcity of fats for the soap industry. And now that glycerol may be produced from the propane of refinery gases, the

complete synthesis of fats from petroleum is possible (119).

Other general synthesis of glycerides involve ester substitution or rearrangement. Thus, an alkyl ester of a fatty acid may be heated with glycerol to produce mono-, di-, or triglycerides by ester exchange (120, 121). Interesterification may also occur during the acylation of a monoglyceride (122) or by heating two different triglycerides (94). Catalysts used include aromatic, aliphatic, or mixed sulfonic acids, Cs, Pb, Sn, Zn, and their compounds; heavy metals and their alloys; or mixtures of these materials (123, 124, 125). Heating fatty acid glycerides with resin acids also results in interesterification (126). Fatty acids have been introduced into fats by heating alone (127, 128), and the replacement of lower by higher fatty acids in fats has been accomplished by heating natural fats with fatty acids containing at least two more carbons than the lowest fatty acid to be replaced, but not more than a total of 18 carbon atoms (129).

Applications

A synthetic drying oil, Synourin, is obtained by the esterification of the dehydrated fatty acids from castor oil. The condensation of a phenol-formaldehyde mixture with the ester of tall-oil fatty acids and glycerol has recently been suggested as a linseed oil substitute (130). Mono- and diglycerides are used in varnishes (131, 132, 133, 134). Alkyd resins (115) resulting from the reaction of glycerol with phthalic anhydride and modified with various fatty acids or oil, form the bases for a large percentage of the baking enamels and quick drying varnishes and enamels. They are also used in the manufacture of printing inks and coatings for moisture-proof paper. Estolides such as are produced by esterifying triricinolein with ricinoleic acid are used as softening agents in the production of plastics (46) and for improving lubricating oils (94). Other glyceride types may also be used as softening agents (128, 135).

The production of edible fats from olive, peanut, and cottonseed oils has been described (136, 99). Mono- and diglycerides of stearic and lauric acids are widely used in the food industry as emulsifying agents, thickeners, stabilizers, surface tension lowering agents, texture improvers, homogenizers, binders, and protective film forming media (137). The products are marketed as mixtures containing soaps and salts as impurities. Several recent patents deal with the preparation and use of mono- and diglycerides in cake or shortening (134).

Among the synthetic glycerides that have been used in pharmacy are salicylic acid esters readily absorbed by the skin (107), glycerophosphates and glycerobophosphate esters of monoglycerides (90), glycerides containing silicon (111, 112) and INTARVIN (triheptadecylin or trimargarin) used in diabetic dietaries. Certain ethylene glycolides and glycerides are used as bacteriocides and bacteriostatic agents (138, 139).

Mono- and diglycerides are used as emulsifying agents for oil-in-water or water-in-oil emulsions, depending upon the balance of the compound. Those which stabilize the water-in-oil type are used as water absorbents in ointment bases (51, 140). The emulsifying properties of monoglycerides are improved by esterification with sulfuric acid (44, 132). Polyglycerol esters are also used in cosmetics (142, 143), and condensation products of halogenated aromatic hydrocarbons with triglycerides may be used (141). All these compounds are textile detergents.

Other applications of synthetic glycerides include the uses as insecticides (143, 144), substitutes for camphor with cellulose derivatives (88), plasticizers (89, 144), "factice-like" polymers (145), modifiers of waxes, gums and resins (88), and treating agents in the textile industry (109). Moreover, pure synthetic optically active glycerides are now finding use in investigations of intermediary metabolism (24).

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A Rapid Volumetric Test for Anhydrous Soap

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INTRODUCTION

This paper treats of a rapid, volumetric method for determining anhydrous soap. The procedure and equipment are adapted from the Babcock test for butterfat used in the dairy industry.

The test has been given a fair trial for a period of six months in the author's laboratory and has developed to the point where it largely supersedes the long, unwieldy A.O.C.S. ether-extraction method.

EQUIPMENT AND DETAILS OF PROCEDURE

The equipment consists of a hand driven Babcock milk-test centrifuge, a liter Berzelius pyrex beaker which is used as a boiling-water bath,* pyrex test bottles made up according to the specifications listed in the accompanying sketch. The 4 ml. graduated necks of the latter are calibrated at 100°C. to contain milliters at 4°C. Usually a correction factor has to be determined for each test bottle, which should not exceed 1±.004 for the 4 ml. graduation.

The routine of the test is as follows:

Weigh in the tared test bottle a 3.5 to 5 gram sample (depending on anhydrous soap content) to the nearest milligram. Add about 5 ml. (an excess) of 37% hydrochloric acid and place in water bath until fatty acids clarify. Twirling the bottle prevents carbonates from foaming over after addition of acid. Glycerin C.P. at a temperature of 110-115°C. is added from a wash bottle until the fatty acids are brought into the graduated portion of the neck. The test bottle is centrifuged for a few seconds and then placed in the boiling water bath the upper level of which should lie above the column of fatty acids. Equilibrium in temperature between the fatty acids and the boiling water should not take more than 10 or 15 minutes. At the end of this period, the reading is taken. First the test bottle is partially withdrawn to allow the reading of the bottom of the upper meniscus of the fatty acids, then the bottle is completely withdrawn to allow the reading of the bottom of the lower meniscus. The difference between the readings represents the observed volume in milliters, which multiplied by the correction factor of the test bottle gives the actual volume of fatty acids at 100°C./4°C. The actual volume multiplied by a predetermined factor gives the weight of anhydrous soap. The latter factor is derived from the specific gravity of the fatty acids at 100°C./4°C. and the acid value of the fatty acids.

Special technic is required in introducing some soap samples into the test bottle. Flake soap may be finely comminuted. Bar soap can be cut into small strips. Hot neat or kettle soap may be introduced into the tared and stoppered bottle by means of a preheated 10 ml. pipette, the tip of which has been cut off.

Often times the reading of the lower meniscus of the fatty acids is obscured by a layer of organic impurity. A few drops of hot glycerin added just before the reading will separate this layer from the fatty acids and allow a clear reading.

* Pellets of copper wire are useful to prevent "bumping" in the bath.