The Preparation and Properties of Some Synthetic Glycerides. I. Procedures to Minimize Contaminants in Intermediates and Constituent Fatty Acids[1,2]

J. E. JACKSON, State University College, Geneseo, New York and W. O. LUNDBERG, The Hormel Institute, University of Minnesota, Austin, Minnesota

Abstract

The preparation of 1-monotritylglycerol and the debromination of tetrabromostearic acid have been modified to increase the purity of glycerides synthesized by procedures involving these two compounds. Solubility and melting point data showed that ditritylglycerol, formed as a by-product in the reaction between trityl chloride and glycerol, is not readily separable from monotritylglycerol, and its presence is difficult to detect unless special melting point methods are used. To minimize formation of ditritylglycerol, large excesses of glycerol were used in the preparation of monotritylglycerol. In the preparation of linoleic acid from tetrabromostearic acid, formation of *trans* double bonds was reduced to a minimum by increasing the amount of mineral acid used to promote the debromination with zinc dust.

Introduction

OF THE PROCEDURES which have been devised for selective esterification of the hydroxyls of glycerol, one of the most useful for the large-scale preparation of mixed glycerides of the fatty acids is that devised by Helferich and Sieber (1) and studied extensively by Verkade and coworkers (2). Monotritylglycerol is esterified by reaction with the desired fatty acyl chloride; then the trityl (triphenylmethyl) groups are removed by suitable means, leaving free hydroxyls which may be esterified further, as desired, by reaction with a second acyl chloride. If linoleoyl radicals are to be included in the glycerides, they are introduced most conveniently as the tetrabromostearoyl derivative, as suggested by Black and Overly (3).

When monotritylglycerol is the starting material for the synthesis of glycerides, contamination with ditritylglycerol can lead to the formation of monoglycerides. These impurities interfere with the characterization of the desired glycerides, and tend to obscure the extent and effects of acyl migration. Additional impurities in the glycerides, caused by isomerization of double bonds, may result when linoleic acid is introduced as the tetrabromide which is debrominated after formation of the glycerides.

Purification of 1-monotritylglycerol by taking it up in absolute ethyl alcohol and filtering off the insoluble 1,3-ditritylglycerol, as described by Verkade, has only limited value. Temperature, concentration, and the relative amounts of ditritylglycerol and monotritylglycerol have been found to affect the separation. Therefore, to minimize the formation of ditritylglycerol in the reaction between triphenylchloromethane (trityl chloride) and glycerol, at least 10 moles excess of glycerol was used. The recrystallized product was considered to be pure monotritylglycerol when it was completely soluble in an equal weight of absolute ethyl alcohol at room temperature and showed 2 polymorphic forms on melting.

To minimize the second source of contamination—formation of *cis-trans* isomers (4) during debromination of tetrabromostearoyl radicals—the extensive low-temperature crystallization used by Matthews, Brode, and Brown (5) to prepare pure linoleic acid, of course is not applicable to mixed glycerides. Hence, methods of debromination were investigated to determine if a procedure could be found which would eliminate or minimize geometric isomerization of the double bonds.

Debrominating in an inert atmosphere, and subsequently handling the freed linoleic acid only under carbon dioxide or nitrogen, has been shown to reduce or eliminate conjugation and *trans* isomerization incident to oxidation (6). A further substantial reduction in *trans* double bonds has been obtained by proper choice of the solvent in which the debromination is effected (7). Nevertheless, some formation of *trans* double bonds still occurred during the debromination. This was minimized in large batches and virtually eliminated in the debromination of small amounts of tetrabromostearic acid, as described below, by increasing the amount of hydrochloric acid used to promote the reaction with zinc dust.

Experimental

Trityl Chloride (Triphenylchloromethane). Trityl chloride was prepared by the method described by Gatterman (8), and by the method described by Bachmann in "Organic Syntheses" (9).

1-Monotritylglycerol. Distilled glycerol (1440 g, 15.66 moles) was dissolved in 1500 ml of pyridine which had been dried by distillation 3 times from phosphorous pentoxide and collected over phosphorous pentoxide. To this solution was added slowly, over a period of 20 min, a solution of 620 g (2.22 moles) of trityl chloride, mp 112–112.7C, also dissolved in 1500 ml of dry pyridine. During the addition of the trityl chloride solution the reaction mixture was swirled gently in an ice bath. The resulting clear, yellow-green solution was left standing 48 hr at room temperature in a tightly-stoppered Erlenmeyer flask.

Increments of about 600 ml each then were poured into 1.5 liter portions of water in a 4 liter separatory funnel and extracted with diethyl ether. The combined ether extracts were washed 5 times with 1.5 liter portions of water, 3 times with 1 liter portions of ice-cold 0.5 N sulfuric acid, once with 1 liter of water, twice with 1 liter portions of 5% sodium bicarbonate, and 3 times, finally, with 1 liter portions of water. This washing procedure effectively removed all traces of the pyridine. The pyridine-free ether solution was dried over anhydrous sodium sulfate, filtered, and the ether removed under the vacuum of a water aspirator.

The residue was a soft, spongy, light-yellow solid

[1] From thesis submitted by J. E. Jackson in partial fulfillment of requirements for degree of Doctor of Philosophy, University of Minnesota, 1953. This work was supported in part by a grant from Archer-Daniels-Midland Co.

[2] Publication No. 4264, Agricultural Experiment Station, University of Minnesota.

which weighed 729 g (95% of theory). This was recrystallized from 4 vol of benzene at room temperature, filtered by suction, and washed on the filter with a small volume of petroleum ether. When free from solvent, the precipitate weighed 541 g (72.5% of theory). It melted at 109.7–110.1C after it had been converted to the higher-melting polymorphic form by holding it at a temperature of 70–75C (just below its softening point) for 2 hr. Heated directly from room temperature, this sample softened at about 80C, and melted at temperatures from 93–105C, depending upon the heating rate. Using a thrust-in melting point procedure, the sample melted at 92C. This is the melting point of the lower-melting polymorphic form of 1-monotritylglycerol.

1,3-Ditritylglycerol. To 23 g (0.25 mole) of distilled glycerol in 400 ml of dry pyridine were added slowly, with swirling to mix reactants, 149 g (0.535 mole) of trityl chloride. The trityl chloride dissolved readily. In about 1 hr a heavy precipitate of fine needles began to form. The mixture was left standing for several days at room temperature in a tightly-stoppered flask.

The reaction mixture then was washed and dried as described for the preparation of monotritylglycerol. To the resulting diethyl ether solution an equal volume of petroleum ether was added to bring the total volume to about 600 ml, and the ditritylglycerol was crystallized at 5C. The precipitate was recrystallized at room temperature from a mixture of 300 ml of acetone and 500 ml of absolute ethyl alcohol.

Two crops of crystals were collected. The first crop weighed 52.2 g (36% of theory), and melted at 174.0–174.4C. Cooled rapidly to room temperature and then remelted, this sample melted at 177–178C. The second crop of crystals weighed 20.8 g (14.4% of theory), melted at 170.5–172C, and remelted at 171–173C.

Debromination of Tetrabromostearic Acid. Debrominations were carried out in a 3-neck round-bottom flask fitted with a motor-driven stirrer and a reflux condenser. A stream of nitrogen was introduced by means of a long glass tube extending down through the condenser to nearly the surface of the reaction mixture. Reactants were introduced through the third neck of the flask.

In a typical debromination, 5 g of tetrabromostearic acid (recrystallized from hot ethylene chloride to a melting point of 115.5–115.8C) and 50 ml of diethyl ether were charged to the flask and the measured amount of mineral acid was poured in as the mixture was stirred. (The optimum amount for minimal formation of *trans* bonds was 1.4 ml of concentrated hydrochloric acid per 5 g of tetrabromide. (See also Results and Discussion.) Five g of zinc dust were added rapidly in small increments as stirring was continued vigorously under a stream of nitrogen. Depending somewhat on conditions, the reaction usually was rapid and exothermic. After all the zinc dust had been added, usually in 3–5 min, and the vigor of the reaction had subsided, stirring was continued at ambient temperature, with a slow stream of nitrogen over the surface of the solution, for at least 45 min. Then the reaction mixture was poured through a filter into a separatory funnel containing water, washed free of mineral acid, dried over sodium sulfate, filtered again, and the solvent removed at the water aspirator. All of the later operations were also conducted under nitrogen.

This basic procedure was modified as required to determine the effect of varying: (1) the temperature, from ice bath temperature to reflux; (2) the order of adding reactants; (3) the amount and kind of mineral acid used as catalyst; (4) the batch size; (5) the nature of the solvent (diethyl ether, methyl alcohol, acetic acid, and petroleum ether were investigated).

In those experiments in which mineral acid was not used to promote the debromination, the reaction mixture was filtered into dilute hydrochloric acid in a separatory funnel and shaken well with the acid to decompose any zinc soaps before proceeding with the isolation of the linoleic acid.

Iodine value (I.V.) (Wijs, 30 min) of the samples ranged from 180–181.5 (theory for linoleic acid, 181.5). Melting points ranged from −5.5 to −3.5C, depending upon the amount of *trans* bond contamination (see Fig. 1). These were determined by introducing a column of linoleic acid approximately 5 mm long into a standard melting point capillary tube by means of a medicine dropper drawn out to a thin capillary. The samples were frozen overnight at −17C, then melted by slowly raising the temperature in a dry ice-acetone bath.

Debrominations in methyl alcohol were similar with respect to the amount of materials used and the method of adding reactants, but these reaction mixtures were stirred only 30 min. under nitrogen at room temperature and refluxed an additional 30 min to complete esterification. After extracting and washing the ester, as described for the free acid, I.V. was determined. I.V. ranged from 171.3–172.5 (theory for methyl linoleate, 172.8). This ester was converted to the free acid, the acid value was determined to make sure that saponification was complete, and small samples of the free acid were frozen overnight in melting point capillaries, for melting point determinations, as described above.

Estimates of the *trans* double bonds present in the samples were made from spectra obtained with a Perkin-Elmer Model 21 Recording Infrared Spectrophotometer. These estimates were based on the infrared absorption of the esters at 968 $cm.^{-1}$, the wavenumber characteristic of an isolated *trans* double bond (4,10). A good correlation, within experimental error, was found between the melting points of the linoleic acid samples and the estimated *trans* bond content of the corresponding methyl esters, as shown in Figure 1.

Results and Discussion

The Tritylglycerols. It was found that 1-monotritylglycerol is soluble at room temperature in an equal weight of absolute ethyl alcohol, but solution is incomplete when as little as 0.1% of 1,3-ditritylglycerol is present as a contaminant. At 5C, 1-monotritylglycerol remained completely soluble in absolute ethyl alcohol, whereas 1,3-ditritylglycerol was virtually insoluble. However, when 1-monotritylglycerol was contaminated with 10–33.3% of 1,3-ditritylglycerol and the mixtures taken up in 10 vol of ethyl alcohol, from 3.4–7.5% of the ditritylglycerol was not separated, the amount of unseparated ditritylglycerol increasing as the amount originally present increased. Mixtures containing less than 10% of ditritylglycerol in monotritylglycerol were found to be completely soluble in 5 vol of absolute ethyl alcohol.

While pure monotritylglycerol readily shows evidence of polymorphism, in the presence of traces of 1,3-ditritylglycerol only the higher melting polymorph is exhibited. As a result, impure monotritylglycerol tended to have a melting point which was approximately correct for the higher-melting polymorphic

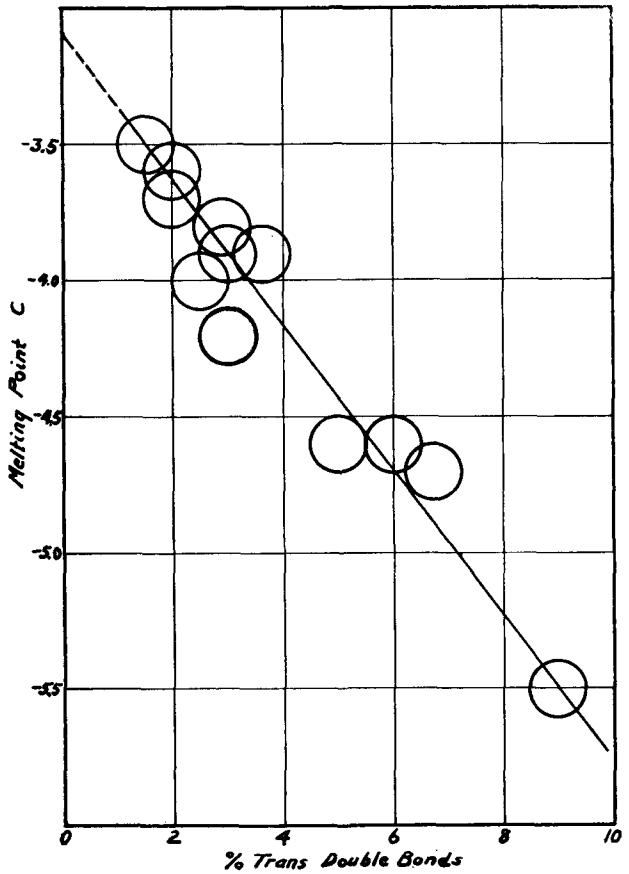

FIG. 1. Effect of *trans* double bond contamination on the melting point of linoleic acid.

form of the pure compound. In contrast, pure monotritylglycerol melted over a long range of temperature (from 92–103/106C, depending on heating rate) if the melting point was determined without the special handling required to show the presence of polymorphic forms.

The melting point curve for the known mixtures of 1-monotritylgylcerol and 1,3-ditritylglycerol (Fig. 2) shows that monotritylglycerol contaminated with as much as 10% of ditritylglycerol will not necessarily have a melting point which is significantly different from that for the pure monotritylglycerol. Analogous uncertainties appeared in the cooling curves of these same mixtures. Up to 5% contamination with ditritylglycerol, there was only one plateau in the cooling curve of the contaminated monotritylglycerol. At 5% contamination, two brief plateaus occurred. When more than 5% of ditritylglycerol was present, the mixture became an intractable, viscous syrup when melted.

The significance of the change in slope in the curve of Figure 2 in the vicinity of 25–35% ditritylglycerol is not known.

Formation of Linoleic Acid. Two percent or less of *cis-trans* isomer was formed during the debromination of 5 g samples of tetrabromostearic acid in diethyl ether in the presence of an amount of hydrochloric acid equivalent to one-half of the zinc dust required for the debromination. However, about 3% of *cis-trans* isomer was formed when 50 g of tetrabromostearic acid were debrominated in a reaction mixture in which all other components also were increased five-fold. The amount of *cis-trans* isomer also increased slightly when the debromination was carried out in

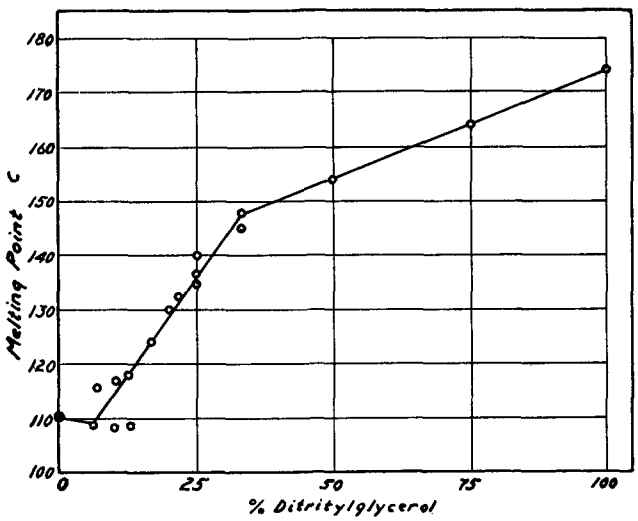

FIG. 2. Melting points of mixtures of 1-monotritylglycerol and 1,3-ditritylglycerol.

either more dilute or more concentrated ether solutions when the zinc dust was added slowly over a period of 50 min, or when the mineral acid was added drop-wise to the slurry of tetrabromostearic acid and zinc dust in ether.

Results comparable to those obtained by using hydrochloric acid as a catalyst were obtained by substituting either sulfuric acid or phosphoric acid diluted to the same normality and added to the reaction mixture in the same stoichiometric amount. Substituting dry hydrogen chloride did not change the course of the reaction, although the dry gas could be used in a much higher concentration than the aqueous acid. Concentrations of concentrated hydrochloric acid greater than those specified above caused an increase in the amount of *cis-trans* isomer.

Increasing the reaction temperature caused an increase in *trans* double bonds when the solvent was methyl alcohol, but had only a negligible effect when the reaction solvent was diethyl ether. Thus Rollet's original reaction conditions (11), using methanol as solvent and dry hydrogen chloride as the catalyst at reflux temperature, are particularly unfavorable for the preparation of linoleic acid free of *cis-trans* isomer.

ACKNOWLEDGMENT

Infrared analyses and advice and assistance in interpreting data by J. R. Chipault, University of Minnesota.

REFERENCES

1. Helferich, B., and H. Sieber, Z. Physiol. Chem. *170*, 31 (1927).
2. Verkade, P. E., and J. van der Lee, Proc. Acad. Sci., Amsterdam, *37*, 812 (1934); C.A. *29*, 2915 (1935). P. E. Verkade, J. van der Lee, and W. Meerburg, Rec. Trav. Chim. *54*, 716 (1935). P. E. Verkade and J. van der Lee, *Ibid. 55*, 267 (1936). P. E. Verkade, J. van der Lee, and W. Meerburg, *Ibid. 56*, 365 (1937). P. E. Verkade, W. D. Cohen, and A. K. Vroege, *Ibid. 59*, 1123 (1940). P. E. Verkade *Ibid 62*, 393 (1943). P. E. Verkade, J. van der Lee, and W. Meerburg, *Ibid. 56*, 613 (1937).
3. Black, H. C., and C. A. Overly, J. Am. Chem. Soc. *61*, 3051 (1939). U.S. Patent 2,408,905 (October, 1946).
4. Jackson, J. E., R. F. Paschke, W. Tolberg, H. M. Boyd, and D. H. Wheeler, JAOCS *29*, 229 (1952).
5. Matthews, N. L., W. R. Brode, and J. B. Brown, J. Am. Chem. Soc. *63*, 1064 (1941).
6. O'Connor, R. T., D. C. Heinzelman, Maizie Caravella, and S. T. Bauer, Oil and Soap *23*, 5 (1946).
7. Kaufmann, H. P., and H. E. Mestern, Ber. *69B*, 2684 (1936). J. S. Frankel and J. B. Brown, J. Am. Chem. Soc. *65*, 415 (1943). W. R. Brode, J. W. Patterson, J. B. Brown, and J. S. Frankel, Ind. Eng. Chem., Anal. Ed., *16*, 77 (1944).
8. Gatterman, L., "Laboratory Methods of Organic Chemistry," pp. 346–7, Macmillan & Co., Ltd., London, 1948.
9. Bachmann, W. E., "Organic Syntheses," vol. 23, p. 100, John Wiley & Sons, New York, 1943.
10. Ahlers, N. H. E., R. A. Brett, and N. G. McTaggart, J. Appl. Chem. (London) *3*, 433 (1953).
11. Rollet, A., Z. Physiol. Chem. *62*, 410 (1909).

[Received December 1, 1962—Accepted March 6, 1963]