

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SWIFT & COMPANY]

Synthetic Glycerides of Unsaturated Fatty Acids. I. Mono- and Trilinolein

BY HOWARD C. BLACK AND CHARLES A. OVERLEY

Glycerides of known constitution of the saturated fatty acids have been prepared by Fischer¹ and King² in high degrees of purity. However, the synthesis of pure glycerides of unsaturated acids has been complicated by the difficulty encountered in preparing the acid chlorides of such acids.

In the present paper a new method for the synthesis of unsaturated glycerides is proposed. It consists of the preparation of glycerides from the acid chlorides of bromine addition products of unsaturated fatty acids and subsequent removal of the bromine to yield the unsaturated glycerides. Linoleic acid has been selected for the initial work because of the ease of preparation and purification of its crystalline tetrabromide. Also recent work has shown quite definitely that the debromination of the tetrabromide yields only the natural linoleic acid.^{3,4} In addition, linoleic esters are of interest because of their biological importance.⁵ The acid chloride of the tetrabromo derivative of linoleic acid was prepared in crystalline form. From it the mono- and triglycerides were prepared according to the methods of Fischer as described by King and debrominated to yield mono- and trilinolein, respectively.

Experimental

Tetrabromostearic acid was prepared by bromination of the acetone-soluble fraction⁴ of cottonseed oil fatty acids. The method of Rollet⁶ as modified by McCutcheon³ was employed, m. p. 115.5°.

9,10,12,13-Tetrabromostearoyl Chloride.—Eighty grams of tetrabromostearic acid in a round-bottomed flask under reflux condenser was placed in an oil-bath at 120°. When the acid had melted 15 g. (1.2 mole) of thionyl chloride was added in small portions through the condenser over the period of an hour. Only slight darkening occurred. It was allowed to cool to room temperature and stand overnight. The oil was taken up in 250 ml. of anhydrous petroleum ether and placed at -26° for several hours. The shiny, white plates which separated were filtered in the freezer and washed with cold petroleum ether until most of the excess thionyl chloride was removed. The product was carefully dried *in vacuo*: yield 78.0 g.; m. p. 59.5–60.0°; total halogen as Br, 59.92; calcd., 60.28. The m. p. was not changed by subsequent recrystallizations

from anhydrous ether or petroleum ether. In comparison to other aliphatic acid chlorides this product is quite stable.

Mono-(9,10,12,13-tetrabromo)-stearin.—To a cold mixture of 10.0 g. (0.075 mole) of acetoneglycerol and 9.6 g. (0.075 mole) of quinoline in a glass-stoppered Erlenmeyer flask was added in small portions with cooling and shaking 45 g. (0.073 mole) of 9,10,12,13-tetrabromostearoyl chloride dissolved in 20 ml. of dry chloroform. The mushy mixture was allowed to stand for forty-eight hours at room temperature. The material was then taken up in 150 ml. of cold ether and washed successively several times with cold 0.5 *N* sulfuric acid, saturated sodium bicarbonate solution and water. After being dried over anhydrous sodium sulfate the ether solution was allowed to stand at -26°. The gummy precipitate was filtered and recrystallized from 1:1 ether-petroleum ether at -26°: yield 35.5 g.; m. p. 51.5–52.0°. The monoglyceride was liberated from the acetone condensation product by dissolving 35 g. of the latter in 300 ml. of ether, cooling in an ice-bath and adding 300 ml. of cold concentrated hydrochloric acid in portions with vigorous shaking. The mixture was let stand overnight at -26° and the semi-crystalline solid filtered and washed free of chlorides with cold water. It was dried *in vacuo* and recrystallized from 500 ml. of ether at 0°. The product appeared as plates when examined under the high power microscope: yield 26 g.; m. p. 101.5–102.0°; Br, 47.60, calcd., 47.45.

Tri-(9,10,12,13-tetrabromo)-stearin.—To a cold mixture of 2.2 g. (0.024 mole) of glycerol and 9.6 g. (0.075 mole) of quinoline in a glass-stoppered Erlenmeyer flask was added with shaking and cooling 45 g. (0.073 mole) of 9,10,12,13-tetrabromostearoyl chloride in 30 ml. of dry chloroform. The semisolid mass was let stand at room temperature for two days and taken up in 600 ml. of ether and washed successively with 0.5 *N* sulfuric acid, saturated sodium bicarbonate solution and water. The ether solution was dried over anhydrous sodium sulfate and placed at 0°. The crystals which separated appeared to be needles under low power and long thin plates under high. They were recrystallized from ether: yield 30.5 g.; m. p. 81.0–81.5°; Br, 51.97, calcd., 52.18.

Debromination of Mono-(9,10,12,13-tetrabromo)-stearin.—This was carried out by treating 20-g. lots of the tetrabromo derivative with 20 g. of 30-mesh zinc and 50 ml. of anhydrous alcohol. The zinc had been washed with dilute hydrochloric acid, then with water and carefully dried. The flask was gently warmed in a water-bath until the beginning of the vigorous exothermic reaction, which was controlled by cooling the flask with ice. Finally the alcohol was refluxed for half an hour and the zinc removed by filtration. The flask and zinc were washed with 150 ml. of anhydrous petroleum ether. The filtrate and washings were washed several times with water and finally dried over anhydrous sodium sulfate and evaporated *in vacuo*. The nearly colorless oil was taken up in 30 ml. of a 1:1 ether-petroleum ether mixture and let stand at -26° overnight. Shiny crystals separated.

(1) Fischer, *Ber.*, **53**, 1621 (1920).

(2) Averill, Roche and King, *THIS JOURNAL*, **51**, 866 (1929).

(3) McCutcheon, *Can. J. Research*, **B16**, 158 (1938).

(4) Riemenschneider, Wheeler and Sando, *J. Biol. Chem.*, **127**, 391 (1939).

(5) Burr and Burr, *ibid.*, **86**, 587 (1930).

(6) Rollet, *Z. physiol. Chem.*, **62**, 410 (1909).

After being filtered and dried they melted to a colorless viscous oil at room temperature: yield 8.9 g.; iod. value 142.1; calcd. for monolinolein 143.3; sap. value 158.5, calcd. 158.3; n_{20}^D 1.4758; m. p. determined by placing a drop in an ordinary m. p. tube and letting stand in a beaker of alcohol at -26° for several hours and then warming slowly, 14.0 – 15.0° . When the debromination was carried out with $0.4 N$ alcoholic hydrochloric acid, 0.5 g. of an oil was isolated from the filtrate; iod. value 158.3; sap. value 178.0; n_{20}^D 1.4636.

Debromination of Tri-(9,10,12,13-tetrabromo)-stearin.

—This was carried out as described for the monoglyceride. The product did not crystallize at -26° . It had the following constants: iod. value 171.2; calcd. for trilinolein 173.3; sap. value 191.2, calcd. 191.5; n_{20}^D 1.4709; m. p. determined as above, -5.0 – 4.0° . Nothing distilled when the oil was heated to 250° in a vacuum of 0.5 mm.

Rebromination of the Linoleins.—Three grams of trilinolein dissolved in 50 ml. of petroleum ether took up bromine at 20° to yield 4.5 g. of gummy material which could not be crystallized. Three grams of monolinolein was dissolved in 50 ml. of petroleum ether and bromine dissolved in petroleum ether added at 20° with stirring; 2.5 g. of gummy material separated, m. p. 92 – 95° . Recrystallization from ether yielded crystals melting at 101.5 – 102.0° , mixed m. p. with mono-(9,10,12,13-tetrabromo)-stearin, 101.5 – 102.0° . An oil which could not be crystallized was isolated from the filtrate.

Saponification of the Linoleins and Rebromination of the Acid.—Six grams of each of the glycerides was let stand overnight with 75 ml. of 5% alcoholic sodium hydroxide and the fatty acids isolated by acidification and extraction with petroleum ether. Five grams of acid from each of the glycerides was brominated in 80 ml. of petroleum ether at 20° , yielding 4.5 g. of crystals melting at 115.5° . Likewise 5 g. of linoleic acid obtained by debromination of tetrabromostearic acid was brominated to yield 4.5 g. of crystals melting at 115.5° ; mixed m. p. with the tetrabromide of the acid isolated from the linoleins 115.5° .

Discussion

The advantage of the present method for preparation of unsaturated glycerides is that the double bonds are protected from polymerization and oxidation until the final step, thus yielding the glycerides with a minimum amount of impurities. The method is limited to the glycerides of the unsaturated fatty acids, the bromine derivatives of which yield the natural acids on debromination. That the unsaturated glycerides synthesized in this case very probably contain the natural linoleic acid is indicated by the identity of the tetrabromides of the acid isolated from the glycerides with the tetrabromide of natural linoleic acid. The yields of solid tetrabromide obtained on bromination of the acids isolated from the glycerides agree with those reported for the bromination of natural linoleic acid.^{3,4} At least the position of the double bonds

has not been shifted and it is unlikely that *cis-trans* isomerization has occurred since several investigators have shown that the acid regenerated by debromination of the solid tetrabromo derivative is identical with natural linoleic acid.^{3,4,6,7,8} There is no reason to assume that debromination of the acid radical in the glycerides should produce a different configuration than debromination of the free acid.

When the debromination was carried out in neutral solution there was no evidence of inter-esterification, but when alcoholic hydrochloric acid was used with the monoglyceride a small amount of material with constants corresponding roughly to those of ethyl linoleate was isolated. Attempts to carry out the debromination in certain other solvents were unsuccessful.

Rebromination of the unsaturated glycerides produced the anticipated results. When linoleic acid is brominated, approximately a 50 – 50 yield of solid and liquid tetrabromide is obtained.^{3,4} There is no reason to assume that the bromination of linoleic glycerides should proceed differently. Indeed, bromination of monolinolein yielded a 40 – 45% yield of the solid bromo monoglyceride, as well as some oily material. Since no homogeneous product could be isolated from the bromination of trilinolein, it is reasonable to assume that both the liquid and solid derivatives of the fatty acid radicals were formed. Suzuki⁹ has reported the isolation of the bromine addition products of several triglycerides from fish oils. He did not report a derivative of trilinolein and only a few addition products of mixed glycerides of linoleic acid.

Summary

A new method for the synthesis of unsaturated glycerides has been proposed. It consists of the preparation of glycerides from acid chlorides of bromine addition products of unsaturated fatty acids and subsequent removal of the halogen to yield the unsaturated glycerides. The method has been applied to mono- and trilinolein.

In addition to mono- and trilinolein, 9,10,12,13-tetrabromostearoyl chloride and mono- and tri-(9,10,12,13-tetrabromo)-stearin have been synthesized.

CHICAGO, ILLINOIS

RECEIVED AUGUST 5, 1939

(7) Birose, *Nat. and Appl. Bull. Univ. Philippines*, **2**, 103 (1932).

(8) Brown and Frankel, *THIS JOURNAL*, **60**, 54 (1933).

(9) Suzuki and Yokoyana, *Proc. Imp. Acad. (Japan)*, **3**, 526 (1927); also later papers.