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Preparation of Saturated and Unsaturated Symmetrical Monoglycerides

BY JAMES B. MARTIN

RECEIVED JUNE 24, 1953

A new method for the synthesis of 2-monoglycerides is reported. The acid-labile benzylidene group of 1,3-benzylidene-2-acylglycerols is split off by reaction with boric acid; the resulting borate esters are hydrolyzed by washing with water to yield 2-monoglycerides. Unsaturated symmetrical monoglycerides, namely, 2-monoölein, 2-monoelaidin and 2-monolinolein are reported as new compounds.

Existing methods[1,2] for the preparation of aliphatic 2-monoglycerides (2-MG) employ hydrogenolysis to remove groups blocking the 1,3-positions of glycerol after the acyl group has been introduced into the 2-position. However, hydrogenolysis cannot be used for the preparation of the heretofore unreported unsaturated 2-monoglycerides due to hydrogenation of the ethylenic bonds.

Boric acid was found to be ideally suited for the removal of benzylidene groups from 1,3-benzylidene-2-acylglycerols (acid-labile acetals). The facility of boric acid for forming esters under mild conditions leads to the formation of borate ester groups in the 1,3-positions. The borates are readily hydrolyzed on contact with water to yield symmetrical monoglycerides (MG).

Of various solvents tried, ethyl borate proved superior as a solvent for the reactants since it reduces reaction time and temperature and improves the purity of the product.

The 1,3-benzylidene 2-acyl glycerol and boric acid are dissolved in triethyl borate, the solvent is evaporated and the reactants heated at 100° for 10 minutes. The product is dissolved in ethyl ether and water-washed, after which the MG component is recovered by crystallization from petroleum ether. Symmetrical MGs prepared by this reaction are of a high purity. The impurities consisting of unsymmetrical MG are generally in the range of from 1.5 to 2.5% in the 2-MG from the boric acid reaction, as contrasted with a minimum concentration of 2.5% in the 2-MG obtained through hydrogenolysis.

Experimental

Materials. 1,3-Benzylideneglycerol was prepared by the method of Hibbert and Carter[3] as modified by Jackson.[4]

1,3-Benzylidene-2-acylglycerols were prepared by acylation of 1,3-benzylideneglycerol (20% excess) with acid chlorides in the presence of an equivalent quantity of pyridine in chloroform solution. After 24 hr. at 16° the sample was dissolved in 2.5 volumes of ethyl ether and washed with an equal volume of ice-cold 0.4% hydrochloric acid followed by washing with water until neutral. The solvent was evaporated under vacuum. The palmitoyl and elaidoyl derivatives after two crystallizations from 10 volumes of ethanol at 0° melted at 62.4 and 40.3° (uncor.), respectively, as compared with 63.5° and 43.5–44.0° reported in the literature.[1,5] Impurities in the acyl components are probably responsible for the lower m.p.'s. The oleyol and linoleoyl derivatives were not crystallizable and possessed acid values of 15–20. The presence of 10% fatty acid as an impurity did not have any adverse effect on the preparation of 2-MG.

Triethyl borate was prepared by the method of Webster and Dennis.[6]

Boric Acid.—Merck Reagent Grade.

Method. Boric Acid Cleavage of 1,3-Benzylidene-2-acylglycerol to obtain 2-Monoglycerides.—A quantity of 0.038 mole of 1,3-benzylidene-2-acylglycerol was dissolved in 50 ml. of triethyl borate and 0.070 mole of finely powdered boric acid was added. The mixture was heated at 100° until the reactants were dissolved (3–5 min.). The solvent was evaporated while heating under vacuum (2–5 mm. press.) and the heating under vacuum at 100° was continued for 10 minutes after the bulk of the solvent had been removed. The sample was cooled and dissolved in 500 ml. of ethyl ether. The ether solution was washed 4 times with 200-ml. portions of water, dried briefly over anhydrous sodium sulfate, filtered, and the ether evaporated under vacuum at a maximum temperature of 25°. The residue was dissolved in 500 ml. (or more if needed) of Skellysolve F, using gentle warming if necessary to obtain complete solution. Crystallization was induced by cooling to a satisfactory temperature depending upon the nature of the acyl group. 2-Monopalmitin crystallized at 0°, 2-monoelaidin at −15°, 2-monoölein at −25° and 2-monolinolein at −35°. The crystals were collected on a suction filter and dried under vacuum at a temperature below the melting point.

Optimum Reaction Conditions.—1,3-Benzylidene-2-palmitoylglycerol was employed for the general investigation of the boric acid cleavage of the benzylidene group from the glyceride.

The cleavage reaction occurred at elevated temperatures without the use of a solvent, but use of solvents capable of dissolving the reactants resulted in marked improvements in the purity and yield of 2-MG. Triethyl borate as a solvent gave good yields of high purity 2-MGs at a minimum reaction temperature and time. (Dioxane is an alternate solvent for the two reactants, but is inferior to triethyl borate in reducing the reaction temperature and time.)

TABLE I

YIELD AND PURITY OF 2-MONOPALMITIN PREPARED BY BORIC ACID CLEAVAGE UNDER VARIOUS REACTION CONDITIONS

Reaction conditions[a] Temp., °C.	Time, min.	Molar ratio[b]	2-MG yield, %	1-MG impurity,[c] %
100	10	0.51	46	1.6
100	10	1.00	53	2.4
100	10	1.36	42	1.5
100	15	1.37	63	2.9
100	30	1.39	73	8.4
100	10	2.03	75	4.7
100	10	3.09	82	6.5
125	5	1.41	63	14.0

[a] In this series, the quantities of the reactants were reduced to approximately $1/15$ of those given in the description of the method. [b] Molar ratio designates the number of moles of H_3BO_3 per mole of 1,3-benzylidene-2-palmitoylglycerol. [c] 1-MG impurity was determined by a micro periodic acid oxidation procedure developed from the method of Pohle and Mehlenbacher.[7]

(1) M. Bergmann and N. M. Carter, *Z. physiol. Chem.*, **191**, 211 (1930).

(2) B. F. Daubert, THIS JOURNAL, **62**, 1713 (1940).

(3) H. Hibbert and N. M. Carter, *ibid.*, **51**, 1601 (1929).

(4) F. L. Jackson, Ph.D. Thesis, "Synthetic Glycerides, Preparation and Properties of a Series of Symmetrical Monoöleo-Disaturated Triglycerides," University of Pittsburgh, 1943.

(5) B. F. Daubert, THIS JOURNAL, **67**, 1033 (1945).

(6) S. H. Webster and L. M. Dennis, *ibid.*, **55**, 3233 (1933).

(7) W. D. Pohle and V. C. Mehlenbacher, *J. Am. Oil Chem. Soc.*, **27**, 54 (1950).

TABLE II

PREPARATIONS OF UNSATURATED 2-MONOGLYCERIDES BY BORIC ACID CLEAVAGE OF 1,3-BENZYLIDENE-2-ACYLGLYCEROLS

Compound	Mole ratio, H_3BO_3/1,3-benzylidene 2-acyl glycerol	Yield, %	M.p., °C.[a] (uncor.)	Analytical data: Hydroxyl val.[b] Found	Hydroxyl val.[b] Calcd.	Iodine val.[c] Found	Iodine val.[c] Calcd.	Acid val.	1-MG Content, % Without isom.[d]	1-MG Content, % With isom.[e]
2-Monoölein	1.8	65	23.2	313	315	70.7	71.2	0.8	4.13	85.0
2-Monoölein	1.8	58	23.5	317	315	...	...	0.6	2.0	..
2-Monoelaidin	1.1	27	53.7	...	...	69.2	71.2	...	1.4	84.6
2-Monoelaidin	1.4	86	..	...	...	...	...	...	2.1	
2-Monoelaidin	(Composite of (3 prepns.)		54.2	314	315	...	...	0.2	1,2	..
2-Monolinolein	1.8	30	8.9	...	...	141.0	143.2	...	1.8	83.1

[a] Values obtained on crystals from petroleum ether except for 2-monolinolein which was melted and chilled before melting point measurement. [b] Determination of hydrogen evolved by reaction with lithium aluminum hydride. [c] Wijs method. [d] According to Pohle and Mehlenbacher, ref. 7, with reduction in concn. of reagents to permit determinations on 3–9 mg. quantities of 1-MG. [e] Isomerization of 2-MG to 1-MG by treatment with 56% aqueous perchloric acid, followed by analysis for 1-MG content, according to a preliminary report in a paper by F. H. Mattson, *et al.*, *J. Nutrition*, **48**, 335 (1952), and a forthcoming paper by the author; the isomerization technique applied to pure 1- or 2-MG results in a 1-MG content of 85 ± 3%.

Boric oxide was practically inactive while metaboric acid was essentially identical in splitting activity to the more readily available orthoboric acid.

The effects of variations in reaction temperature and time as well as in the molar ratio of the reactants are indicated by the data in Table I.

The data illustrate the importance of keeping the reaction temperature and time as low as possible to minimize the formation of the 1-MG impurity.

The boric acid cleavage of the benzylidene group from the glyceride has not been found to follow a simple stoichiometric behavior, but this may be the result of several factors, namely: (1) the polyfunctionality of boric acid, (2) the reaction as used is not carried to completion, and (3) boric acid interacting with triethyl borate may yield a mixture of ethylboric acids of variable composition, which are the active agents in the reaction. Molar quantities in the range of 0.5 to 2.0 moles of boric acid per mole of 1,3-benzylidene-2-acylglycerol give good yields of 2-MG.

Unsaturated 2-Monoglycerides from Boric Acid Cleavage of 1,3-Benzylidene-2-acylglycerols.—The properties of 2-monoölein, 2-monoelaidin and 2-monolinolein prepared by this method are shown in Table II.

Acknowledgment.—The assistance of Messrs. R. G. Folzenlogen and R. A. Volpenhein in this work is gratefully acknowledged.

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[CONTRIBUTION FROM THE CHEMICAL DIVISION OF THE PROCTER & GAMBLE CO.]

The Equilibrium between Symmetrical and Unsymmetrical Monoglycerides and Determination of Total Monoglycerides

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RECEIVED JULY 6, 1953

Perchloric acid as a catalyst isomerizes 1- and 2-monoglycerides in chloroform solution to an equilibrium mixture containing about 90% 1-monoglyceride. 2-Monoglycerides do not react with periodic acid commonly used for the determination of monoglycerides; however, by application of the periodate analysis before and after perchloric acid isomerization, it is possible to determine 1-monoglycerides and total monoglycerides present in a mixture from which the original 2-monoglyceride content is readily obtained by difference. After isomerization, the total monoglyceride content of the fat is calculated by multiplying the per cent. 1-monoglyceride from periodic acid oxidation by a factor of 1.15 to convert from the equilibrium composition and correct for the slight effect of side reactions. The method is applicable to both saturated and unsaturated compounds; no interference from other fatty substances has been observed.

Acid and alkaline media as well as fusion are known to promote the isomerization of 2-monoglycerides (2-MG) to 1-monoglycerides (1-MG).[1] Monoglycerides dissolved in purified chloroform containing 0.5% ethanol are isomerized rapidly and reproducibly at room temperature with an aqueous 56% perchloric acid solution as a catalyst to yield an equilibrium mixture of the fatty MG isomers containing 90–92% 1-MG and 10–8% 2-MG. Evidence for the existence of an equilibrium in this concentration range has not been reported previously, but Verkade[2] has indicated that aromatic monoglycerides exist in equilibrium at a composition of 88% 1-MG and 12% 2-MG.

The perchloric acid-catalyzed isomerization is applicable as a step in the determination of total MG in fats containing 2-MG. The 2-MG content of a fat is the difference between total MG calculated after isomerization and the 1-MG content determined before isomerization. Equilibrium formation by isomerization makes about 85% of the total MG present in the reaction mixture accessible to periodic acid oxidation, and the total MG value is obtained by using a factor of 1.15 to correct for the equilibrium composition and the slight interference from side reactions. The monoglycerides can be saturated or unsaturated and other fatty materials have not been found to interfere with the isomerization.

(1) B. F. Daubert and C. G. King, THIS JOURNAL, **60**, 3003 (1938).

(2) (a) P. E. Verkade, private communication; see also, *Chim. Ind.*, **69**, 239 (1953). (b) P. E. Verkade and O. E. van Lohuizen, *Proc. Roy. Dutch Acad. Sci.* (to be publ.).