707. *Glyceride Synthesis by Direct Esterification.*

By L. Hartman.

Glycerides of known structure have been synthesised, without recourse to protecting groups, by making use of differences in reactivity of primary and secondary hydroxyl groups of glycerol. α-Monoglycerides and αα'-diglycerides of a single acid are prepared from acyl chlorides and glycerol in homogeneous chloroform solution obtained with the aid of *NN*-dimethylformamide. Monoacylation was assisted by the use of complexing agents. Diglycerides containing two different acids are obtained by treating a monoglyceride with another fatty acid chloride. Triglycerides containing one unsaturated acid are prepared by a three-stage process.

Most syntheses of glycerides are based on the use of protecting groups; the present communication reports syntheses based on the difference in reactivity of primary and secondary hydroxyl groups of glycerol. Although the introduction of certain protecting groups, *e.g.*, triphenylmethyl, depends on the greater reactivity of the primary hydroxyl groups, there seems to be no direct experimental proof of the differing reactivities of hydroxyl groups in glycerol towards fatty acids. Some conclusions can be drawn from the classic work of Menshutkin,[1] who found that the rate of esterification depended on the type of the hydroxyl group: *e.g.*, esterification of ethylene glycol with acetic acid was faster than of propylene glycol, and of glycerol faster than of erythritol or mannitol. The comparative reactivities of primary and secondary hydroxyl groups in glycerol are difficult to establish directly owing to acyl migration in β-monoglycerides and αβ-diglycerides, though this only accentuates the final effect of the α-position's being favoured in comparison with the β-position. Whereas these considerations apply to esterification, as distinct from acylation, the work of Norris and his associates [2] on the reactivity of various alcohols with *p*-nitrobenzoyl chloride has shown that in this respect there is no fundamental difference between the two reactions.

Some use of the different reactivity of α- and β-hydroxyl groups of glycerol has been made in the past. α-Monoglycerides were prepared by Hilditch and Rigg [3] by direct esterification of fatty acids with a large excess of glycerol in phenol, but the products were impure, probably owing to the side reactions with phenol. αα'-Diglycerides were obtained by transesterification of glycerol αα'-disulphate with fatty acids [4] and by esterifying monoglycerides with fatty acid chlorides in the presence of pyridine or with fatty acids in the presence of acid catalysts.[5]

In the present work, fatty acid chlorides were used instead of fatty acids to obtain a greater range of products and better yields. Experimental conditions were established for the preparation of α-monoglycerides, αα'-diglycerides with one and two component acids and triglycerides with one unsaturated acyl group. The preparation of β-monoglycerides and αβ-diglycerides seems to be impracticable by direct esterification without the use of protecting groups.

The reaction of fatty acid chlorides and a large excess of glycerol resulted in formation of α-monoglycerides and some diglycerides. A homogeneous mixture of glycerol and of the solution of fatty acid chlorides in chloroform—an essential feature of the method—was ensured by the use of *NN*-dimethylformamide which seems to be the best cosolvent. To keep diglyceride formation to a minimum it was advisable to reduce the reactivity of one primary hydroxyl group with a suitable chelating agent: 1 mol. of potassium thiocyanate, urethane, or triethyl phosphate proved satisfactory; on the other hand, addition of boric acid resulted in a complete conversion of acid chlorides into acids, and use of urea led to a certain amount of insoluble products.

Diglycerides containing residues of a single acid were prepared by direct acylation of a theoretical quantity of glycerol in homogeneous solution, obtained also with the aid of *NN*-dimethylformamide. Diglycerides containing different acyl groups resulted from the reaction between a monoglyceride and a fatty acid chloride in approximately equimolar proportions. The preparation of such diesters by heating α-monoglycerides with fatty acids in the presence of toluene-*p*-sulphonic acid as catalyst proved impracticable owing to migration of acyl groups.

Of the triglycerides with one unsaturated component acid the three isomeric triglycerides containing stearoyl, palmitoyl, and oleoyl residues are of special interest because of their frequent occurrence in natural products. It seems that the only successful synthesis of these glycerides in the past was by Verkade [6] with the aid of triphenylmethyl compounds. They have now been prepared by three-stage direct acylation. In addition, the preparation of glycerol α-laurate α'-oleate β-palmitate is reported. In order to introduce the third acyl group in these compounds refluxing of the chloroform solution had to be resorted to since at room temperature the reaction was too slow.

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[1] Menshutkin, *Ann. Chim. Phys.*, 1880, **20**, 289; 1881, **23**, 14; *Ber.*, 1880, **13**, 812, 814.

[2] Norris and Ashdown, *J. Amer. Chem. Soc.*, 1925, **47**, 837.

[3] Hilditch and Rigg, *J.*, 1935, 1714.

[4] Grün, *Ber.*, 1905, **38**, 2284.

[5] Malkin, Shurbagy, and Meara, *J.*, 1937, 1409.

[6] Verkade, *Rec. Trav. chim.*, 1943, **62**, 393.

EXPERIMENTAL

Materials.—Fatty acids and their chlorides. Saturated fatty acids were prepared from commercial samples by fractional distillation and crystallisation of methyl esters, and conversion into free acids. Oleic acid was prepared from olive oil by a similar method and had an iodine value of 90·1 (calc. 89·9) and m. p. 13·2°.

In preparing fatty acid chlorides the chief aim was to dispense with the time-consuming distillation of crude products. In the case of saturated fatty acids this was achieved by refluxing the acids for 2 hr. with an equal weight of thionyl chloride previously distilled over quinoline and linseed oil.[7] The acyl chlorides remaining after the removal of the excess of reagent *in vacuo* were pale and were used immediately after preparation.

A pale oleoyl chloride could not be obtained in this way, and therefore oleic acid was refluxed with an equal weight of oxalyl chloride in light petroleum for 2 hr., which resulted in an almost colourless product.

NN-*Dimethylformamide.* This was shaken with anhydrous calcium sulphate and siphoned off when required.

Chloroform. B.P. chloroform was washed with water, dried with calcium chloride and potassium carbonate, and distilled over phosphoric oxide. 0·1 ml. of butanol per l. was added and extended the storage life to several months without interfering appreciably with the esterification of glycerol.

Pyridine. Pyridine was used in preference to quinoline because of the greater ease of its removal with mineral acids. It was dried by refluxing with barium oxide and kept over solid potassium hydroxide.

Glycerol. This was of analytical reagent grade. It was made anhydrous by heating it to 160° before use with continuous stirring. Higher temperatures were avoided in view of the recent findings [8] that dehydration occurs above 170°.

Preparation of α-Monoglycerides.—The preparation of α-monopalmitin is given as an example: Glycerol (18·4 g., 0·2 mole) and potassium thiocyanate (19·5 g., 0·2 mole) were heated in a porcelain dish with stirring to 160° to dehydrate both reagents. The hot mixture was poured into a glass-stoppered bottle and 40 ml. of dry dimethylformamide were added followed by anhydrous pyridine (1·6 g., 0·02 mole) and dry chloroform (30 ml.). To the mixture, cooled to about 10°, palmitoyl chloride (5·5 g., 0·02 mole) in chloroform (10 ml.) was added dropwise with shaking. The initial turbidity usually disappeared after the mixture attained room temperature, otherwise it was removed by addition of chloroform. Next morning ethyl ether (200 ml.) was added and the solution washed 3 times with water to remove potassium thiocyanate, then with 0·5N-hydrochloric acid and with water. The solvents were distilled off. The monopalmitin crystallised from ether (yield, 4·7 g., 71%; m. p. 76·5—77°).

Similar results were obtained by using urethane (19·8 g., 0·2 mole) or triethyl phosphate (36·4 g., 0·2 mole) instead of potassium thiocyanate. In each case the complex-forming agent was heated with glycerol to 160°.

Monolaurin, m. p. 62—63° (64%), monomyristin, m. p. 70° (69%), and monostearin, m. p. 81° (71%), were obtained by a similar procedure, but the amounts of dimethylformamide and chloroform were varied to provide for different solubilities. The α-monoglyceride content in these products was determined by the periodate method of Pohle and Mehlenbacher,[9] suitably modified, and was found to be 98—99%.

αα'-Diglycerides with One Component Acid.—Anhydrous glycerol (0·92 g., 0·01 mole) was dissolved in dimethylformamide (2 ml.), chloroform (15 ml.), and pyridine (5 ml.) in a glass-stoppered bottle. Palmitoyl chloride (5·5 g., 0·02 mole) in chloroform (10 ml.) was added dropwise with shaking and cooling in water. Next day ethyl ether was added and the ethereal solution was washed with 0·5N-sulphuric acid, 5% aqueous potassium carbonate, and water. The product crystallised from alcohol and hexane (3·8 g., 67%; m. p. 73·5—74°) (Found: C, 73·7; H, 12·0. Calc. for $C_{35}H_{68}O_5$: C, 73·9; H, 12·1%).

Distearin was prepared similarly from 0·92 g. of glycerol and 6·05 g. of stearoyl chloride, the yield being 4·5 g. (72%) and the m. p. 80° (Found: C, 74·8; H, 12·4. Calc. for $C_{39}H_{76}O_5$: C, 74·9; H, 12·3%).

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[7] Fieser, " Experiments in Organic Chemistry," Heath & Co., New York, 1941, 2nd edn., p. 381.

[8] Hauschild and Petit, *Bull. Soc. chim. France*, 1956, 878.

[9] Pohle and Mehlenbacher, *J. Amer. Oil Chemists' Soc.*, 1950, **27**, 54.

The m. p.s approximate to those reported by Porck and Craig.[10]

αα′-Diglycerides with Two Component Acids.—Glycerol oleate palmitate, oleate stearate, oleate laurate, and palmitate stearate were prepared from corresponding α-monoglycerides and oleoyl or stearoyl chloride. Preparation of the α-palmitate α′-oleate is given as an example: To α-monopalmitin (3·6 g., 0·011 mole) in chloroform (30 ml.) containing pyridine (1 g., 0·012 mole), oleoyl chloride (3 g., 0·01 mole) in chloroform (10 ml.) was added with shaking and cooling. The mixture was left overnight and treated as described for diglycerides with one component acid. After crystallisation from alcohol and 1 : 1 alcohol–light petroleum, 4·1 g. (69%) of diglyceride, m. p. 44·5—45°, were obtained (Found: C, 75·0; H, 12·1%; I val., 42·3. Calc. for $C_{37}H_{70}O_5$: C, 74·7; H, 11·9%; I val., 42·7).

Triglycerides with One Unsaturated Acid Component.—*α-Oleate β-palmitate α′-stearate.* The intermediate products were α-monostearin and the α-oleate α′-stearate prepared as described before. The latter (3·1 g., 0·005 mole) in chloroform (6 ml.) and pyridine (5 ml.) was treated with palmitoyl chloride (1·5 g.) in chloroform (3 ml.) with cooling. The mixture was refluxed on a water-bath for 4 hr., then worked up as for diglycerides and the residue, after the removal of solvents, was crystallised from 4 : 1 acetone–light petroleum at 0° (yield, 3·0 g., 70%; m. p. 40—40·5°) (Found: C, 76·9; H, 12·0; I val., 28·9. Calc. for $C_{55}H_{104}O_6$: C, 76·7; H, 12·2%; I val., 29·5).

α-Oleate α′-palmitate β-stearate. The α-oleate α′-palmitate (3 g., 0·005 mole) was treated with stearoyl chloride (1·7 g.), as above, giving the triglyceride (3·0 g., 70%), m. p. 39—40° (Found: C, 77·0; H, 12·3%; I val., 29·8).

β-Oleate α-palmitate α′-stearate. The α-palmitate α′-stearate (3 g., 0·005 mole) and oleoyl chloride (1·6 g.) yielded triglyceride (3·1 g., 72%), m. p. 37—38° (Found: C, 76·8; H, 12·0%; I val., 29·1).

As reported by Verkade[6] the three isomeric triglycerides when mixed in pairs gave m. p. depressions. Verkade's observation that the first of the three acquires an electrical charge when rubbed was also confirmed.

α-Laurate α′-oleate β-palmitate. The α-laurate α′-oleate (2·7 g., 0·005 mole) was refluxed with palmitoyl chloride (1·5 g.). After the usual purification 2·6 g. (67%) of triglyceride were obtained, having m. p. 29·5° (Found: C, 75·8; H, 11·9%; I val., 33·3. Calc. for $C_{49}H_{92}O_6$: C, 75·7; H, 11·9%; I val., 32·7).

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[10] Porck and Craig, *Canad. J. Chem.*, 1955, **33**, 1286.