851. *The Use of Trifluoroacetic Anhydride in the Synthesis of Glycerides*

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Most reliable syntheses of glycerides involve the use of acyl halides. Reacting these with blocked glycerol derivatives has permitted the preparation of all types of glyceride, in most cases using pyridine or quinoline as a solvent. However, it has been shown that the best results are obtained by this method only if long reaction times [1] (up to 72 hr.) are used, and this, coupled with the liberation of hydrogen chloride, often results in acyl migration. In addition, some acyl halides are surprisingly difficult to prepare, so that alternative methods are desirable.

Bourne, Stacey, Tatlow, and Tedder [2] showed that glycerol reacts directly with a fatty acid at room temperature when these two compounds are dissolved in trifluoroacetic anhydride. The investigations reported in this Note have extended the method to the preparation of 1- and 2-monoglycerides and some di-unsaturated triglycerides, using blocked glycerols as appropriate.

The yields obtained by using trifluoroacetic anhydride are lower than those quoted for most other methods of preparation, but it must be borne in mind that the latter are based not on the weight of acid used but on that of the acid chloride. The preparations of the 2-acyl dioleins are also significant since they indicate that the reaction conditions are sufficiently mild to reduce acyl migration to a minimum.

In general, the method has the advantage that the purified fatty acids may be used directly in the synthesis of glycerides, thus eliminating the loss inherent in the conversion

[1] F. H. Mattson and R. A. Volpenheim, *J. Lipid Res.*, 1961, **2**, 58.
[2] E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J.*, 1949, 2976.

of the acid into its halide. Unfortunately, this loss is largely offset by the cost of the trifluoroacetic anhydride.

Experimental.—In all the preparations, the acids were recrystallised until their m. p.s corresponded with those recorded in the literature, and the trifluoroacetic anhydride was redistilled over phosphorus pentoxide immediately before use. 1,2-Isopropylideneglycerol was prepared by the method of Malkin and el Shurbagy,[3] and 1,3-benzylidene glycerol by that of Bergmann and Carter.[4]

All the apparatus was oven-dried before use and preparations involving oleic acid were carried out in an atmosphere of nitrogen.

The purity of 1-monoglycerides was determined by the method of Pohle and Mehlenbacher [5] and of the 2-monoglycerides by perchloric acid isomerisation [6] followed by the same determination of the resulting 1-monoglycerides.

Preparation of 1-monoglycerides (Table 1). The calculated quantity of the appropriate fatty acid was dissolved in trifluoroacetic anhydride, the mixture set aside at room temperature for 30 min., and the required amount of 1,2-isopropylideneglycerol added. The reaction vessel was stoppered and set aside for 1 hr., after which the mixture was poured into aqueous sodium carbonate solution to hydrolyse the excess of trifluoroacetic anhydride and neutralise any free acid.

The product was extracted with chloroform, washed, dried (Na_2SO_4), and the solvent removed at room temperature under reduced pressure. The 1,2-isopropylidene-3-acylglycerol so obtained was converted into 1-monoglyceride without further purification.

The 1,2-isopropylidene blocking group was removed, using the method of Hartman,[7] by heating with finely powdered boric acid in 2-methoxyethanol for 30 min. The mixture was dissolved in diethyl ether, washed thoroughly with water to hydrolyse the borate esters, and the ether solution dried (Na_2SO_4). After removal of the ether, the monoglyceride was recrystallised twice from a mixture of diethyl ether and light petroleum (b. p. 40—60°).

Preparation of 2-monoglycerides (Table 1). A method similar to that used to prepare 1-monoglycerides was adopted, but because of the reduced reactivity of the secondary hydroxyl group of glycerol, it was necessary to reflux 1,3-benzylideneglycerol with the mixture of acid and trifluoroacetic anhydride for 5—15 min., the time being increased with increase in molecular weight of the acid. The 2-acyl derivative thus formed was worked up as in the previous preparations, except that the 1,3-benzylidene group was removed by the method of Martin,[6] by heating with boric acid and using tri-n-propyl borate as the solvent in place of the recommended triethyl borate. Although it is slightly more difficult to remove tri-n-propyl borate from the mixture owing to its higher boiling point, there appear to be no other disadvantages in its use.

After removal of the solvent under reduced pressure, the mixture was again worked up as previously, with final recrystallisation from light petroleum (b. p. 60—80°).

Preparation of 1-acyl 2,3-dioleoyl and 2-acyl 1,3-dioleoyl triglycerides. The calculated quantity of oleic acid was dissolved in trifluoroacetic anhydride and set aside at room temperature for 30 min. After the solution had been cooled to 0°, a weighed amount of the appropriate 1- or 2-monoglyceride was added in small portions; the mixture was then saturated with nitrogen and set aside in the stoppered reaction vessel for 24 hr. After neutralisation with aqueous potassium carbonate solution the pale yellow oil was extracted with chloroform. The extract was washed with water and dried (Na_2SO_4), and the solvent removed at room temperature under reduced pressure in a stream of nitrogen.

The crude triglycerides were purified chromatographically on a silicic acid column (prepared by the method of Hirsch and Ahrens [8]) using as eluents 200 ml. of 4% diethyl ether in light petroleum (b. p. 40—60°) followed by 8% diethyl ether in light petroleum (b. p. 40—60°). The solvent was removed as before, and the triglyceride (Tables 2 and 3) recrystallised from diethyl ether cooled to below −20°.

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[4] M. Bergmann and N. M. Carter, *Z. physiol. Chem.*, 1930, **191**, 211.
[5] W. D. Pohle and V. C. Mehlenbacher, *J. Amer. Oil Chemists' Soc.*, 1950, **27**, 54.
[6] J. B. Martin, *J. Amer. Chem. Soc.*, 1953, **75**, 5482.
[7] L. Hartman, *J.*, 1959, 4134.
[8] J. Hirsch and E. H. Ahrens, *J. Biol. Chem.*, 1958, **233**, 311.

TABLE 1

Preparation of 1- and 2-monoglycerides

Acyl group	Lauroyl	Myristoyl	Palmitoyl	Stearoyl
Acid (g.)	0·76	0·87	0·98	1·08
1-Monoglycerides *				
Trifluoroacetic anhydride (ml.)	3·5	4·0	5·0	6·5
Yield of 1,2-isopropylidene-3-acylglycerol (g.)	0·71	0·80	0·85	0·88
Yield of 1-monoglyceride (g.) †	0·60	0·67	0·70	0·72
Purity (%)	98·3	97·9	99·1	99·4
M. p.	62—63°	70—71°	76—77°	81—81·5°
Lit.,[9] m. p.	63°	70—71°	77°	82°
2-Monoglycerides ‡				
Trifluoroacetic anhydride (ml.)	4·0	5·0	6·0	6·5
Yield of 1,3-benzylidene-2-acylglycerol (g.)	0·78	0·82	0·84	1·0
Yield of 2-monoglyceride (g.)	0·51	0·54	0·58	0·68
Purity (%)	98·0	100·0	97·9	100·2
M. p.	50·5°	60°	69°	74°
Lit.,[9] m. p.	51°	61°	69°	74·4°

* From 0·4 g. 1,2-isopropylideneglyercol. † Cleavage with 0·4 g. boric acid. ‡ From 0·55 g. 1,3-benzylideneglycerol. § Cleavage with 0·3 g. boric acid.

TABLE 2

Preparation of 1-acyl 2,3-dioleins using oleic acid (2·1 g.)

Acyl group	Lauroyl	Myristoyl	Palmitoyl	Stearoy
1-Monoglyceride (g.)	0·82	0·91	1·0	1·07
Trifluoroacetic anhydride (ml.)	6·0	6·0	8·0	8·0
Yield of 1-acyl 2,3-diolein (g.)	0·98	1·0	1·2	1·25
M. p.	4·8—5·3°	12·0—13·0°	18·2—18·7°	22·0—23·5°
Lit.,[10] m. p.	5·5—6·5°	12·5—13·5°	18·0—19·0°	22·5—23·5°
Iodine value	62·9	61·0	59·2	57·1
Iodine value (calculated)	63·2	61·1	59·1	57·2
Refractive index, n_D^{25}	1·4602	1·4608	1·4617	1·4626
Lit.,[10] n_D^{25}	1·45932	1·45995	1·46060	1·46190

TABLE 3

Preparation of 2-acyl 1,3-dioleins using oleic acid (1·7 g.)

Acyl group	Palmitoyl	Stearoyl
2-Monoglyceride (g.)	1·0	1·07
Trifluoroacetic anhydride (ml.)	8·0	8·0
Yield of 2-acyl 1,3-diolein (g.)	0·77	0·81
M. p.	5·0—6·0°	10·5—12·5°
Lit., m. p.	−1° to 0° and 19° [11]	14—15° [12]
Iodine value	58·9	56·1
Iodine value (calculated)	59·1	57·2
Refractive index, n_D^{20}	1·4660	1·4672

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