152. *Acyl Migration in Diglycerides.*

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1 : 2- or 1 : 3-Diglycerides, under the influence of heat or in the presence of catalysts, give an equilibrium mixture of the two esters. The effects of temperature and of the substituent acyl groups on the speed of migration have also been studied, and the work has been extended to monoglycerides.

The facility of acyl migration and the high proportion of the 1 : 2-isomers (which can, in most cases, be readily isolated) in the equilibrium mixture are of significance in the synthesis of diglycerides and their further conversion into triglycerides of known configuration. The application to the preparation of pure unsaturated 1 : 2-diglycerides is of particular interest.

Partial glycerides can be converted under certain conditions into isomers or into mixtures of isomers by migration of the acyl groups within the molecule. This has been studied for monoglycerides, *e.g.*, by Verkade and Lohuizen[1] and Martin,[2] but few workers have studied diglycerides. An early report by Grün[3] described the partial conversion of 1 : 3-distearin and 1 : 3-dipalmitin into the 1 : 2-isomers but most workers have been concerned with the change from 1 : 2- to 1 : 3-diglycerides during reaction and it appears to have been assumed that the 1 : 3-diglycerides are inherently more stable.[4] Our interest was aroused when syntheses of triglycerides from 1 : 3-diglycerides yielded products containing the asymmetrical triglycerides as well as the desired symmetrical isomers.

Equilibrium between 1 : 2- *and* 1 : 3-*Diglycerides.*—The work has been facilitated by the recent development of differential thermal analysis. This technique, which has recently been used in the study of fats,[6] depends on the measurement of temperature differences between a control cell and a cell containing a fat, as heat is applied at a constant rate to the system. If the temperature difference is plotted as a function of time over the range within which melting takes place both endothermal effects due to melting and exothermal

Table 1. *Melting points and equilibrium conditions for diglycerides* (3 *hours' heating*).

		M. p.		Equilibrium mixture	
		Chilled melt (D.T.A.[a])	Crystals from solvent (capillary)	Heating temp.	1 : 3-Diglyceride (%)
Distearin	1 : 2	60·5°	68·0°	165°	58
	1 : 3	80·2	80·2		
Dipalmitin	1 : 2	*	62·8	<165	56
	1 : 3	*	73·2		
Dimyristin	1 : 2	*	55·5	<165	~55
	1 : 3	*	65·2		
Dilaurin	1 : 2	21·8	40·8	140	55
	1 : 3	57·7	57·7		
Diolein	1 : 2	−23·9 −13·9	1·9 †	165	53
	1 : 3	25·8	25·8		
Glycerol di-*p*-nitrobenzoate	1 : 2	*	Liquid	160	~60
	1 : 3	*	138		

* Not determined. † Determined by D.T.A. after tempering.
[a] D.T.A. = differential thermal analysis.

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[1] Verkade and Lohuizen, *Proc. k. ned. Akad. Wetenschap.*, 1953, **56**, 324.

[2] Martin, *J. Amer. Chem. Soc.*, 1953, **75**, 5483.

[3] Grün, in Hefter-Schönfeld, " Chemie und Technologie der Fette und Fetteprodukte," Springer, Vienna, 1936, Vol. I, p. 250.

[4] Malkin and Bevan, " Progress in the Chemistry of Fats and Other Lipids," Pergamon, London, 1957, Vol. IV, p. 69; Gunstone, " An Introduction to the Chemistry of Fats and Fatty Acids," Butterworths, London, 1958, p. 89; Deuel, " The Lipids," Interscience, London, 1951, Vol. I, p. 170.

[5] Young and Sallans, *J. Amer. Oil Chemists' Soc.*, 1958, **35**, 392.

[6] Haighton and Hannewijk, *ibid.*, p. 344; Lavery, *ibid.*, p. 418.

effects due to polymorphic transformations are observed. Some curves for the distearins are shown in Fig. 1. 1 : 3-Distearin is characterised by a single sharp endothermic effect on melting (Fig. 1*a*). Heating at 165° gave a second component, and the curve showed two endothermic deflections. Fig. 1*c* shows the result of heating for ½ hr. Little change occurred as a result of further heating. 1 : 2-Distearin (Fig. 1*b*) showed a similar effect, forming apparently the same final mixture. These mixtures were each resolved by crystallisation from light petroleum into two components which were identified as 1 : 2- and 1 : 3-distearin. Starting from 1 : 3-distearin yielded 58·1% of 1 : 3-distearin and 41·9% of 1 : 2-distearin. From 1 : 2-distearin the yields were 58·2% and 41·7% respectively. Mixing 1 : 2- and 1 : 3-distearin in these proportions afforded a curve (Fig. 1*d*) very similar

FIG. 1. (*a*) 1 : 3-*Distearin.* (*b*) 1 : 2-*Distearin.* (*c*) *Migration product* (½ *hr.*) *at* 165°. (*d*) 1 : 2-*Distearin* 43%, *plus* 1 : 3-*distearin* 57%.

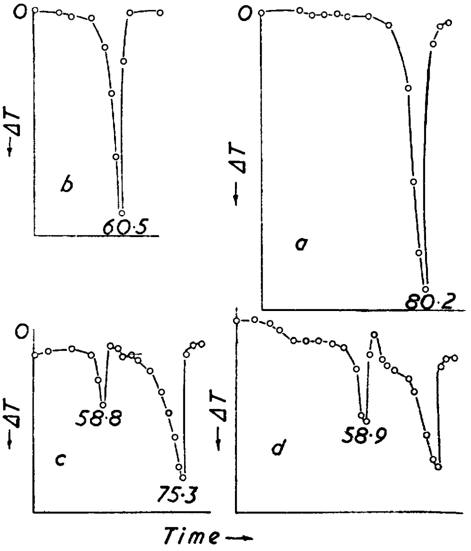
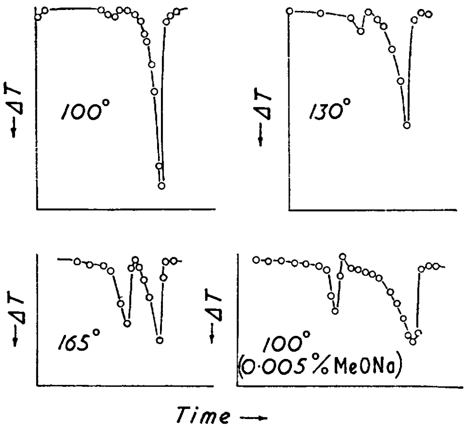


FIG. 2. 1 : 3-*Distearin heated for* ½ *hr.*



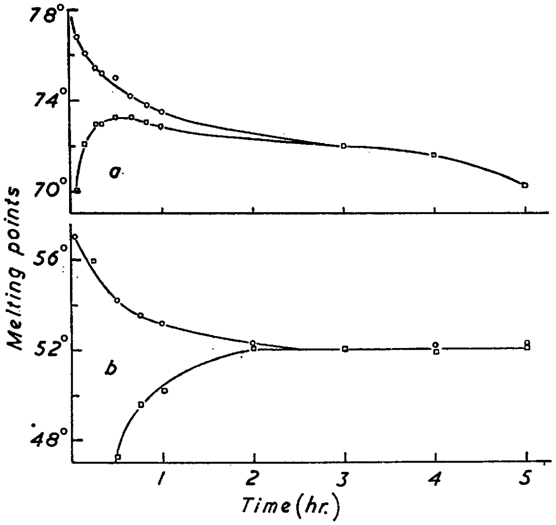


FIG. 3. *Acyl migration in diglycerides.*
O—O (*Upper branch*) 1 : 3-*Diglycerides.*
□—□ (*Lower branch*) 1 : 2-*Diglycerides.*
(*a*) *Distearin at* 165°.
(*b*) *Dilaurin at* 140°.

FIGS. 1 & 3. *Differential thermal analysis.*

to those of the heated samples, and this did not change appreciably on heating. It is evident that an equilibrium mixture of 1 : 2- and 1 : 3-distearin had been established.

The formation of an equilibrium mixture was also demonstrated by a study of the change in melting points on heating. In Fig. 3*a* these are recorded for the distearins and it can be seen that at 165° equilibrium is attained finally after about 3 hours. However, there is then a continued slow fall in melting point: this is thought to be due to true interesterification, or possibly to disproportionation as small amounts of monoglyceride can be detected analytically after several hours' heating. The time required for equilibration depends on the temperature of heating. Only slight changes occur in the differential thermal analysis curves of the distearins when heating was at temperatures below 165° for ½ hr. (see Fig. 2), but slow changes in melting point are evident at temperatures as low as 80°. The rate of change at these low temperatures is increased considerably by the presence of catalysts, either basic (*e.g.*, sodium hydroxide or methoxide) or acidic (*e.g.*, toluene-*p*-sulphonic acid). These are effective at concentrations of less than 0·005% (see Fig. 2).

Acyl migration has been studied thus with distearins, dipalmitins, dimyristins, dilaurins, dioleins, and glycerol di-*p*-nitrobenzoates (see Table 1). It appears that equilibrium is attained more readily the shorter the acyl radical (see Fig. 3*b*): the distearins reach equilibrium after 3 hours' heating at 165°, whereas the dilaurins need only be heated for the same time at 140°. This suggests that the short-chain diglycerides such as diacetin and dibutyrin may well be extremely labile. On the other hand, unsaturation has little effect, diolein behaving in a similar way to distearin.

In the aromatic field glycerol 1 : 3-di-*p*-nitrobenzoate was studied as its crystallisation behaviour was more satisfactory than that of the 1 : 3-dibenzoate. The 1 : 3-di-*p*-nitrobenzoate (m. p. 138°), when heated at 160°, showed an asymptotic fall in melting point to about 127°, but, as the corresponding 1 : 2-diglyceride could not be isolated as a solid, evidence of acyl migration in this case remains presumptive. The 1 : 3-diglyceride could be kept at 110° for six days without change in melting point: this implies a greater stability in aromatic than in aliphatic diglycerides, or, alternatively, as the aromatic diglyceride is solid at 110°, that acyl migration takes place only in the liquid state.

A question of interest in synthetic work is the extent to which acyl migration occurs in solution. The system in which hydrogen chloride is present is of particular importance as this has been widely used in the preparation of 1 : 3-diglycerides from 1-triphenylmethyl-2 : 3-diglycerides.[4,7] Conditions analogous to those used in this reaction were reproduced by passing hydrogen chloride through ethereal solutions of 1 : 3- and 1 : 2-distearin at room temperature. After 1 hour the diglycerides were recovered and in each case mixtures were obtained of similar composition to the equilibrium mixtures occurring in the molten state. It is apparent, therefore, that the hydrolysis of 1-triphenylmethyl-2 : 3-diglycerides with hydrogen chloride or similar reagents will result in a mixture of isomers. In a homogeneous system this would contain *ca.* 40% of the 1 : 2-isomer. However, the higher saturated diglycerides are precipitated during the reaction and the system is therefore "directed" in favour of the less soluble isomer, *i.e.*, the 1 : 3-diglyceride. This explains the yields of *ca.* 80% recorded for these compounds.[7] For the unsaturated diglycerides and the lower saturated diglycerides, which remain in solution throughout the reaction, this directing effect will not operate and low yields are to be expected, and, in fact have been reported for dilaurin and dicaprin.

It thus appears probable that the formation of 1 : 3-diglyceride from 1-triphenylmethyl-2 : 3-diglyceride proceeds *via* the 1 : 2-diglyceride which then undergoes acyl migration. Direct formation of 1 : 3-diglyceride from the triphenylmethyl compounds is not excluded by the present work but seems unlikely.

Acyl Migration as a Method of Preparing 1 : 2-*Diglycerides.*—Until recently the preparation of pure samples of diglycerides, especially 1 : 2-diglycerides, had been tedious.

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[7] Verkade, van der Lee, and Meerburg, *Rec. Trav. chim.*, 1935, **54**, 716.

It has now been found that a 1 : 2-diglyceride may be isolated readily from an equilibrium mixture prepared by heating the 1 : 3-diglyceride. The separation depends on the great difference in solubility between the two isomers in light petroleum. Thus from a solution of the equilibrium mixture from 1 : 3-distearin in light petroleum, when cooled to 35°, 1 : 3-distearin, m. p. 79·3°, is precipitated and on further cooling of the filtrate, to 0°, 1 : 2-distearin, m. p. 68°, separates.

Classical methods of preparing 1 : 2-diglycerides depend on the removal, by hydrogenolysis, of protecting groups at the 3-position, as the final stage of the synthesis.[8] This technique is not applicable to the preparation of unsaturated diglycerides and until very recently no method of preparing such compounds was known. Baer and Buchnea[9] recently described the synthesis of D- and L-1 : 2-diolein by a method depending on the reductive debenzylation of optically active glycerol 1 : 2-di-(9 : 10-dibromostearate) 3-benzyl ethers followed by regeneration of the *cis*-double bonds in the diglyceride by the action of zinc in ether. Melting points of the products were not given but identification was by catalytic hydrogenation to D- and L-2 : 2-distearin. Acyl migration has provided a simpler alternative for the preparation of optically inactive 1 : 2-diolein and seems to be the only feasible route for the polyunsaturated 1 : 2-diglycerides.

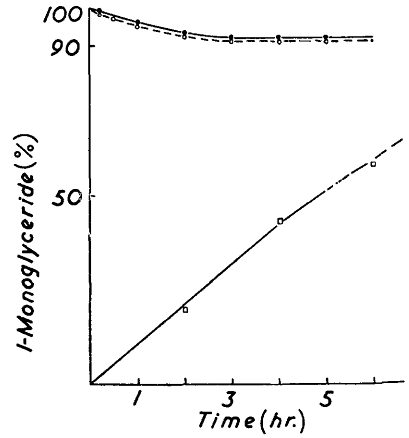

FIG. 4. *Acyl migration in monoglycerides at* 100°.

●—● (*Top curve*) 1-*Mono-olein.*
○ - - - ○ (*Middle curve*) 1-*Monostearin.*
□—□ (*Lower curve*) 2-*Monostearin.*

Acyl Migration in Monoglycerides.—Our studies of pure monoglycerides have been less detailed than those of diglycerides. They show, however, that migration can be induced merely by heat. The rate of conversion of pure 1- or 2-monoglycerides into equilibrium mixtures was followed by analysis for 1-monoglyceride by the periodate method.[10] To ensure that only acyl migration, and not disproportionation, occurred, the total monoglyceride was also determined, by the method of Brokaw *et al.*[11] The results are shown in Fig. 4. Equilibrium mixtures containing about 90% of 1-monoglyceride are formed from pure 1-monostearin or 1-mono-olein in about 3 hours at 100°. Limited studies on the migration in the reverse direction indicate that it is much slower and is incomplete even after 6 hours' heating.

EXPERIMENTAL

Preparations of Saturated 1 : 3-*Diglycerides.*—These were prepared from the corresponding triglycerides by a method basically that of Baur and Lange[12] in which the diglyceride is preferentially crystallised from an interesting mixture of triglyceride, triacetin, and glycerol with sodium methoxide as catalyst. However, instead of destroying the catalyst with acetic acid the reaction mixture was ground to a paste with water. When this paste was then warmed,

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[8] Verkade, Cohen, and Vroege, *Rec. Trav. chim.*, 1940, **59**, 1123.
[9] Baer and Buchnea, *J. Biol. Chem.*, 1958, **230**, 447.
[10] Handschumaker and Linteris, *J. Amer. Oil Chemists' Soc.*, 1947, **24**, 143.
[11] Brokaw, Perry, and Lyman, *ibid.*, 1955, **32**, 194.
[12] Baur and Lange, *J. Amer. Chem. Soc.*, 1951, **73**, 3926.

the diglyceride separated as a molten layer. After being washed twice with water the crude diglyceride was crystallised from ethanol. This modified procedure was adopted as it was found that the original process left traces of sodium methoxide in the product which were sufficient to catalyse acyl migration as described above; in some cases the alkali was only removed after repeated washing of a hexane solution of the diglyceride with water. Our products obtained had the annexed characteristics.

		OH value				OH value	
	M. p.	Found	Calc.		M. p.	Found	Calc.
1 : 3-Distearin ...	80·0°	90·0	89·9	1 : 3-Dimyristin...	65·5	110·0	109·6
1 : 3-Dipalmitin ...	73·2	98·1	98·8	1 : 3-Dilaurin......	58·0°	122·7	123·0

Preparations of Saturated 1 : 2-*Diglycerides.*—1 : 2-Distearin and 1 : 2-dilaurin were prepared by Howe and Malkin's method,[13] hydrogenolysis of the 2 : 3-di-*O*-acylglycerol 1-benzyl ether with palladium black as catalyst giving 1 : 2-distearin, m. p. (capillary) (α) 60·5°, (β) 68·0° (Found: OH value, 90·0. Calc.: OH value, 89·9), and 1 : 2-dilaurin, m. p. (capillary) (α) 20·0°, (β) 39·2° (Found: OH value, 122·5. Calc.: OH value, 123·0).

		Yield	I value	
Monoglyceride	M. p.	(%)	Found	Calc.
1-Mono-olein	35·5°	98·7	70·7	71·4
1-*p*-Nitrobenzoate	108·0	95·0	—	—

		OH value		I value	
Diglycerides	M. p.	Found	Calc.	Found	Calc.
1 : 3-Diolein	25·8°	90·2	90·5	81·4	81·9
1 : 3-Di-*p*-nitrobenzoate	138·0	142·6	143·8	—	—

Preparation of Other 1 : 3-*Diglycerides.*—1 : 3-Diolein and 1 : 3-di-(*p*-nitrobenzoyl)glycerol were prepared from the monoglycerides and acid chlorides by the method of Malkin, Shurbagy, and Meara.[14] The monoglycerides were prepared by the method of Daubert, Fricke, and Longenecker [15] from the acid chlorides and *iso*propylideneglycerol. See annexed Table.

Preparation of 1 : 2-*Diglycerides from* 1 : 3-*Diglycerides by Isomerisation.*—The 1 : 3-diglycerides were heated at 165° for 1 hr. (under nitrogen in the case of diolein). The equilibrium mixtures so formed were dissolved in light petroleum and cooled to precipitate the 1 : 3-diglyceride which was then removed by filtration. The filtrate was cooled further to precipitate the 1 : 2-diglycerides. The temperatures of crystallisation tabulated gave the best results.

	1 : 3-Diglyceride cryst. at	1 : 2-Diglyceride cryst. at	1 : 2-Diglyceride (yield, %)	1 : 3-Diglyceride (yield, %)
Distearin	35°	0°	40	58
Dipalmitin	35	0	44	55
Dimyristin	23	0	45	54
Dilaurin	23	0	44	55
Diolein	−20	(recovered from filtrate by evapn.)	47	47
Di-*p*-nitrobenzoate ...	20 (from $CHCl_3$)	—	—	—

The m. p. of the products are given in Table 1. 1 : 2-Diolein (I value 82·3; OH value 90·4) was further characterised by hydrogenation with palladium black to 1 : 2-distearin, m. p. 68·0° (OH value, 89·6).

Solubilities of Distearin Isomers in Light Petroleum.—Since the diglyceride isomers are separated surprisingly easily by crystallisation from light petroleum, it was of interest to determine their relative solubilities in this solvent. Saturated solutions of 1 : 2- and 1 : 3-distearin were kept overnight at 35°. Samples (5 ml.) of the clear supernatant solutions were then removed and evaporated and the residues dried to constant weight. 1 : 3-Distearin was found to have a solubility of 3·2 g./l. and 1 : 2-distearin had a solubility of 32 g./l.

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[13] Howe and Malkin, *J.*, 1951, 2663.

[14] Malkin, Shurbagy, and Meara, *J.*, 1937, 1412.

[15] Daubert, Fricke, and Longenecker, *J. Amer. Chem. Soc.*, 1943, **65**, 2143.