591. *An X-Ray and Thermal Examination of the Glycerides. Part XI.* The 1 : 2-Diglycerides, and Further Observations on 1 : 3-Diglycerides.*

By R. J. Howe and T. Malkin.

1 : 2-Diglycerides of lauric, myristic, palmitic, and stearic acids are shown to exist in two solid modifications, α and β, for which *X*-ray and m. p. data are reported. The transition α → β is much slower than was found for the more symmetrical 1 : 3-isomers (Part III, *J.*, 1937, 1409). Earlier data for 1 : 3-diglycerides have been extended and reviewed in the light of recent work by Baur, Jackson, Kolp, and Lutton (*J. Amer. Chem. Soc.*, 1949, **71**, 3363).

Our synthetic work on phospholipids (following paper) necessitated the preparation of a series of 1 : 2-diglycerides, and since there does not appear to be any information concerning their polymorphism, we have examined them by means of *X*-rays and cooling and heating curves, in the manner described in Parts I and II (*J.*, 1934, 666; 1936, 1628).

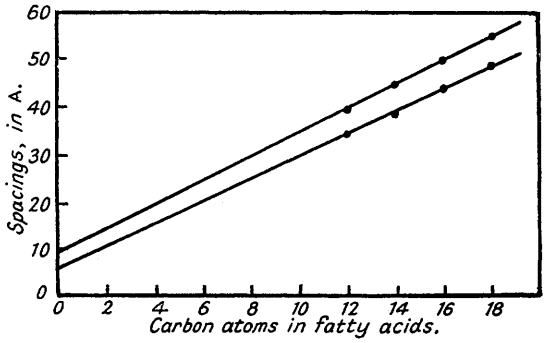
The preparation of these compounds in good yield is a matter of some difficulty, owing to the facile migration of the 2-ester group to the 1(3)-position, particularly in the presence of traces of acids, first shown by Fischer (*Ber.*, 1920, **53**, 1621) who, indeed, took advantage of this migration in his preparation of 1 : 3-diglycerides *via* the intermediate 1 : 2-isomer. This should, therefore,

* Part X, *J.*, 1949, 369.

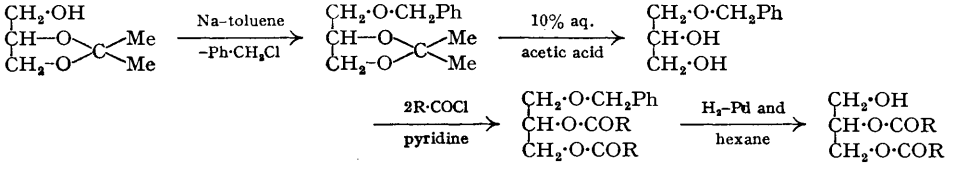
be borne in mind when considering any preparation and description earlier than Fischer's paper (cf. Fairbourne, *J.*, 1930, 368, who reviewed earlier work). The only satisfactory methods of preparation involve (1) protection of one primary hydroxyl of glycerol, (2) complete acylation, (3) removal of the protecting group by catalytic hydrogenolysis. Verkade *et al.* (*Proc. Akad. Wetensch., Amsterdam*, 1937, **40**, 580; *Rec. Trav. chim.*, 1940, **59**, 1123) effected protection with the trityl group, which was removed with a specially activated palladium-black. We find this hydrogenolysis capricious, as did Daubert and King (*J. Amer. Chem. Soc.*, 1939, **61**, 3328). Moreover, removal of the solid by-product, triphenylmethane, by crystallisation reduces the yield, particularly with lower members of the series (C_{14} and C_{12} acids). Daubert and King avoided this by protection with the carbobenzyloxy-group, which, on hydrogenolysis, is converted into toluene, but unfortunately the intermediate carbobenzyloxyglycerol decomposes on distillation, and is therefore difficult to obtain pure. More recently, Sowden and Fischer (*ibid.*, 1941, **63**, 3244) used the 1-benzyl ether of glycerol in the preparation of optically active 1 : 2-diglycerides, and with certain modifications this method gives excellent results. Sowden and Fischer refluxed *iso*propylidene glycerol with powdered sodium over ether for 20 hours, and converted the resulting sodium derivative into the benzyl ether in a yield of 66% by a further 70 hours' refluxing with three molecular proportions of benzyl chloride. The time was shortened and the yield increased to 70% and later to 78% by Baer and Kates (*ibid.*, 1950, **72**, 942) by the use of a sodium–naphthalene reagent (cf. Scott, Walker, and Hansley, *ibid.*, 1936, **58**, 2442;

FIG. 1.

Long spacings of 1 : 2-*diglycerides.*



1938, **60**, 951). We now find that by using for the preparation of benzyl ethers the general method of Van Duzee and Adkins (*ibid.*, 1935, **57**, 147), which involves the use of powdered sodium under toluene, yields of 80—85% of the benzyl ether can be obtained in a few hours, only one molecular proportion of benzyl chloride being used. The yield in the next stage is also improved by using 10% aqueous acetic acid to remove the *iso*propylidene group, a method used by Baer and Fischer (*ibid.*, 1945, **67**, 2031) in their preparation of monoglycerides. Our method of preparation is outlined below :

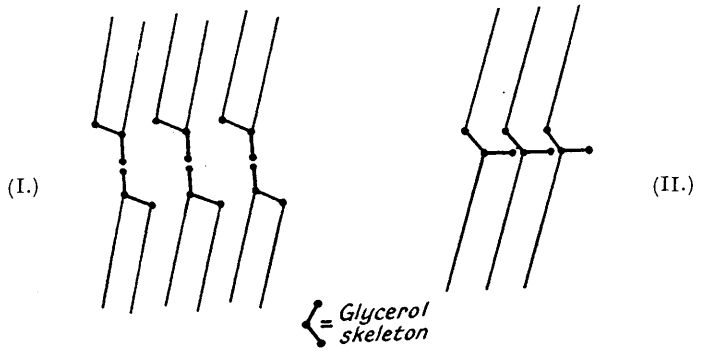


Thermal Examination.—Capillary m. p.s, and cooling and heating curves, show the existence of two solid modifications, a lower-melting α-form and the stable β-form. Solvent-crystallised material melts at the β m. p., and resolidifies at the α m. p., remelting again at the α m. p. The change α → β is very slow, but keeping of α-forms just below their m. p.s overnight brings about the change. Cooling and heating curves normally show only the α m. p. arrests. This behaviour is in sharp contrast to that of the symmetrical 1 : 3-diglycerides, the α-forms of which change so rapidly into β′-forms that their existence can only be indirectly inferred (Part III, *J.*, 1937, 1412). 1 : 2-Diglycerides show spherulite formation when solidified under a cover slip

and viewed between crossed Nicols, but the rippled appearance characteristic of 1 : 3-diglycerides is absent (cf. Part III).

X-*Ray Examination.*—This offered no special difficulty, owing to the relative stability of the α-forms. Long spacings of α- and β-forms were obtained from melted and pressed layers, respectively, and side spacings from thin rods. The long spacings, when plotted against the carbon content of the fatty acid component, fall on two straight lines which cut the axis, C = 0, at ≏ 6·5 and 9·5 A. (Fig. 1). These results best agree with an arrangement of double molecules Fig. 2 (I) lying vertically across (α-form) or inclined at an angle of ≏ 64° (β-form) to the reflecting planes, on the assumption of an angle of 116° between the carbon atoms of the chain. The magnitude of both the α-spacing and the intercepts at C = 0 would appear to rule out an arrangement of single molecules Fig. 2 (II). The side spacings of the α-forms are, within experimental error, identical for the series, and those of the β-forms, although differing slightly

FIG. 2.



Diagrammatic.

amongst themselves, are all of the same type, and quite distinct from those of the 1 : 3-isomers (see Plate, facing p. 2666, and Table I).

1 : 3-*Diglycerides.*—In Part III (*J.*, 1937, 1412), it was shown that the majority of a series of 1 : 3-diglycerides, from didecoin to distearin, existed in both β- and β′-modifications, but that there appeared to be a discontinuity at dipentadecoin, since only one β-form was observed for the higher members. Certain anomalies were also noted regarding the type of side spacings associated with each form, for which no satisfactory explanation could be offered at the time. Considerable light has been thrown on this problem by the recent results of Baur, Jackson, Kolp,

TABLE I.

M. p. and X-*ray data for* DL-1 : 2-*diglycerides.*

	α-Form.			β-Form.				
	M. p.	Long spacing, A.	Side spacing, A.	M. p.	Long spacing, A.	Side spacing, A.*		
						m.	vs.	s.
Dilaurin	20·0°	39·2	4·13	39°	34·1	4·31	4·01	3·79
Dimyristin	37·5	44·4	4·12	54, 59 [3]	38·8	4·31	4·06	3·82
Dipalmitin	50·0	49·3	5·10	63·5, 65—66,[2] 64 [3]	43·5	4·27	4·03	3·76
Distearin	59·5	54·5	4·12	71, 68·5—69 [1] 71·5—72·5 [2]	48·3	4·27	4·05	3·81

[1] Verkade *et al.*, *loc. cit.* [2] Baer and Kates, *loc. cit.* [3] Daubert and King, *loc. cit.*
* m = moderate; vs = very strong; s = strong.

and Lutton (*J. Amer. Chem. Soc.*, 1949, **71**, 3363), who have now observed the missing β-forms for dipalmitin and distearin, and have shown that these compounds frequently crystallise from solvents in the β′-forms, which change into the stable β-forms only when held near the β′ m. p. These results made it clear that there are β′- and β-forms for the whole series; but there still remained some confusion regarding the side spacings. Thus, Baur *et al.* observed two distinct types of side spacings : *a*-type (4·6, v. strong; 3·9, mod.; 3·7, strong) and *b*-type (4·6, v. strong; 3·75, strong), neither of which quite agrees with those described by Malkin and Shurbagy

(Part III, *loc. cit.*), *viz.*, *a*-type (4·6, strong; 3·9, strong; 3·73, strong) and *b*-type (4·6, strong; 3·9, weak; 3·73, strong; 3·6, weak), although there are many points of similarity. Because of these differences, we have re-examined the whole problem, and it appears that there are, in fact, three distinct types of side spacings, *viz.*, the *a*- and *b*-types described in Part III, and the new type observed by Baur *et al.*, which we term *c*-type (Plate, Figs. 6, 7, 8). These occur as follows :

a-Type : β-forms of all odd-acid diglycerides, β′-forms of dipalmitin and distearin.

b-Type : β′-forms of all diglycerides except dipalmitin and distearin.

c-Type : β-forms of all even-acid diglycerides.

b-Type spacings are sometimes very similar to *a*-type, but the latter are distinguished by the equal intensity of the three main lines (see Plate, Fig. 6, *a*-type, and Figs. 9, 10, 11, *b*-type).

M. p. and *X*-ray data for the whole series are given in Table II.

TABLE II.

M. p. and X*-ray data for* 1 : 3*-diglycerides.*

	M. p.		Long spacings, A.		Side spacings, A.*				
	β′.	β.	β′.	β.	β′.			β.	
Didecoin	42°	44·5°	30·5	32·5	*b* 4·65s, 3·93m, 3·7s, 3·46w	*c* 4·55			3·75
Diundecoin	47	49	33·2	35·2	*b* 4·63s, 3·88w, 3·72s, 3·58w	*a* 4·53	3·81		3·66
Dilaurin	54	56·5	35·7	37·4	*b* 4·66s, 3·94m, 3·73s, 3·61vw	*c* 4·6			3·75
Ditridecoin	57	59·5	38·1	40·4	*b* 4·58s. 3·9w, 3·71s, 3·53w	*a* 4·55	3·83		3·68
Dimyristin	63	65·5	40·5	42·6	*b* 4·64s, 3·88m, 3·68s, 3·53vw	*c* 4·57			3·73
Dipentadecoin	66·5	68·5	42·5	45·0	*b* 4·58s, 3·86w, 3·70s, 3·52w	*a* 4·58	3·84		3·68
Dipalmitin	71·5	72·5	44·7	47·5 †	*a* 4·6s, 3·87s, 3·65s	*c* 4·6			3·75
Diheptadecoin	72·5	74·5	47·7	50·3	*b* 4·6s, 3·85m, 3·7s, 3·54w	*a* 4·57	3·82		3·66
Distearin	77	78	49·5	52·8 †	*a* 4·6s, 3·88s, 3·68s	*c* 4·6			3·73

* s = strong; *m* = moderate; w = weak; vw = very weak. All β-side spacings are strong.
† Baur *et al.* find 47·4 and 52·8, respectively.

EXPERIMENTAL.

iso*Propylidene Glycerol* 1-*Benzyl Ether.*—Sodium (11·5 g., 0·5 g.-atom) was granulated under boiling toluene by vigorous stirring, and then cooled, and *iso*propylidene glycerol (Part III, p. 1634) (76 g., 0·58 g.-mol.) was added, in portions, with stirring. The reaction, which was at first vigorous, subsided after a time, and was completed by boiling the toluene to break up unattacked sodium. All the latter had reacted in about an hour. Benzyl chloride (63·25 g., 0·5 g.-mol.) was then added to the gently refluxing, stirred solution during ½ hour, and the heating continued for a further hour. After cooling, precipitated sodium chloride was filtered off and washed with toluene, and after removal of toluene under reduced pressure, the residue was distilled *in vacuo*, yielding a few grams of unchanged benzyl chloride and *iso*propylidene glycerol, boiling up to 110°, and 86·5 g. (78%) of the benzyl ether, b. p. 117—121°/3 mm. Sowden and Fischer (*loc. cit.*) give b. p. 93—96°/0·1 mm.

Glycerol 1-*Benzyl Ether.*—The above *iso*propylidene glycerol ether (17·65 g.) was heated on a boiling-water bath with 10% acetic acid (45 c.c.) with frequent shaking, until the original emulsion had disappeared (2 hours). Acetic acid, water, and acetone were then removed under reduced pressure, and the residue distilled *in vacuo* to yield the glycerol 1-benzyl ether (13 g., 87%), b. p. 140—145°/1 mm.

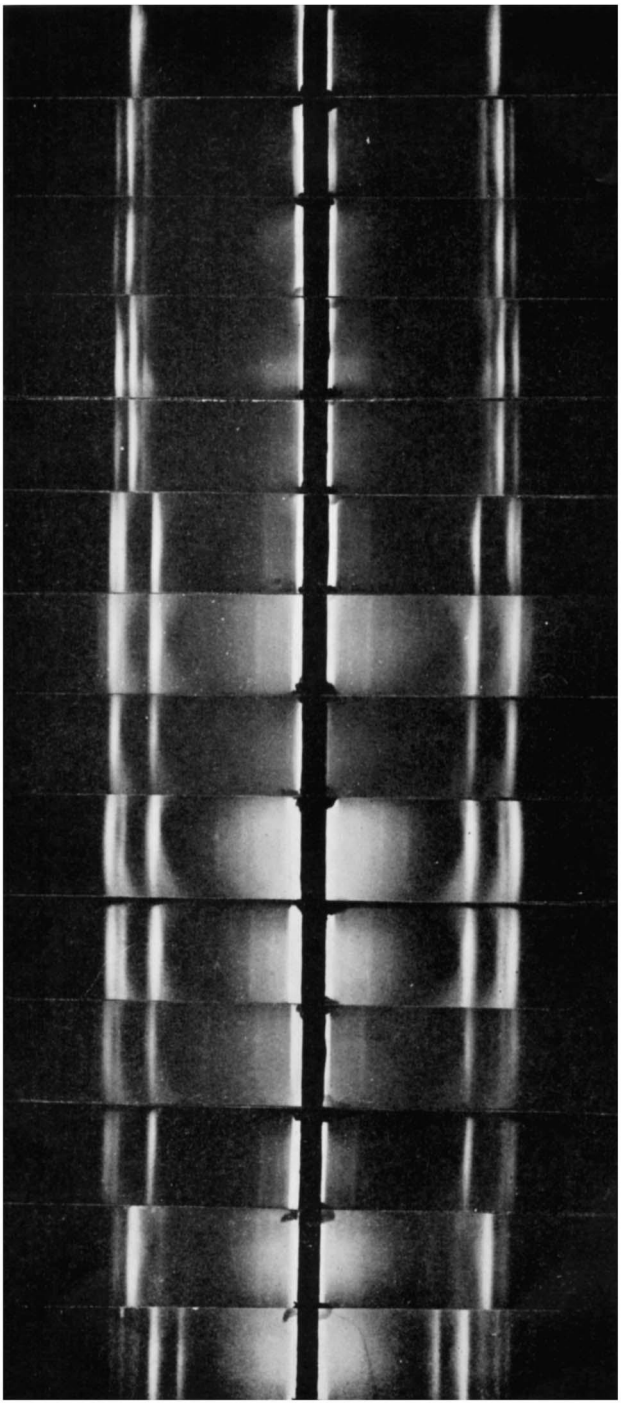
3-Benzyl 1 : 2-*Dipalmitoyl Glycerol.*—The acylation of glycerol 1-benzyl ether followed standard practice and will be described in detail for the dipalmitoyl derivative only. Acid chlorides were prepared by Bauer's method (*Oil and Soap*, 1946, **23**, 1), thionyl chloride being used except for stearic acid, where it is preferable to use oxalyl chloride.

A solution of palmitoyl chloride (16·6 g., 0·03 g.-mol.) in dry carbon tetrachloride (20 c.c.) was added to a mixture of glycerol 1-benzyl ether (5·45 g., 0·03 g.-mol.) and pyridine (4·8 g., 0·03 g.-mol.), dissolved in the same solvent (40 c.c.). The solution became warm, and pyridine hydrochloride separated. After this had been kept overnight at 40°, ether was added, and the ethereal solution was washed successively with 1% aqueous hydrochloric acid, saturated sodium hydrogen carbonate, and water. After drying (Na_2SO_4) and removal of solvent, the solid residue was crystallised twice from ethanol, to yield colourless needle-like crystals (17·5 g., 88%), m. p. 44—45·5°. Baer and Kates (*loc. cit.*) give 48% yield, m. p. 45—46°.

The following 3-benzyl glycerols were prepared in a similar manner : 1 : 2-*Dilauroyl* (78% yield), m. p. 20—21° (Found : C, 74·8; H, 10·9. $C_{34}H_{58}O_5$ requires C, 74·7; H, 10·7%); 1 : 2-*dimyristoyl* (80% yield), m. p. 35—36·5° (Found : C, 75·6; H, 10·9. $C_{38}H_{66}O_5$ requires C, 75·7; H, 11·0%); 1 : 2-distearoyl (83% yield), m. p. 53—55°. These acylations could also be carried out in benzene.

1 : 2-*Dipalmitin.*—The dipalmitoyl intermediate (5 g.), dissolved with gentle warming in *n*-hexane (40 c.c.), and palladium-black (1 g.) (Johnson, Matthey and Co.) were shaken in an atmosphere of hydrogen, until hydrogen uptake, which was at first rapid, had ceased (2 hours) (Found : uptake, 350 c.c. Calc. : 172 c.c.). The dipalmitin was precipitated during hydrogenation in shiny

FIG



1. α-*Form*, 1 : 2-*dipalmitin*.
2. β-*Form*, 1 : 2-*dilaurin*.
3. β-*Form*, 1 : 2-*dimyristin*.
4. β-*Form*, 1 : 2-*dipalmitin*.
5. β-*Form*, 1 : 2-*distearin*.
6. a-*Type* (β-*form of* 1 : 3-*ditridecoin*).
7. b-*Type* (β′-*form of* 1 : 3-*ditridecoin*).
8. c-*Type* (β-*form of* 1 : 3-*dimyristin*).
9. β′-*Form of* 1 : 3-*didecoin*.
10. β′-*Form of* 1 : 3-*dilaurin*.
11. β′-*Form of* 1 : 3-*dimyristin*.
12. β′-*Form of* 1 : 3-*dipalmitin*.
13. α-*Kephalin* (*dipalmitoyl*).
14. β-*Kephalin* (*dipalmitoyl*).

To face p. 2666.

crystals, easily distinguishable from the less crystalline intermediate. After the hydrogen in the apparatus had been displaced by air, the diglyceride was dissolved by warming the solution, and the catalyst was filtered off and washed with hot hexane. On cooling, the solution deposited dipalmitin (4 g., 93%), m. p. 63—64° not improved by further crystallisation. Yields for other members were: *dilaurin* (Found: C, 71·2; H, 11·3. $C_{27}H_{52}O_5$ requires C, 71·0; H, 11·5%), 80%; dimyristin (Found: C, 72·6; H, 11·8. Calc. for $C_{31}H_{60}O_5$: C, 72·7; H, 11·8%), 83%; distearin, 85%. Compared with other members, the m. p. of dimyristin given by Daubert and King (*loc. cit.*) is unusually high. The same catalyst could be used repeatedly if well washed with hexane, an advantage in view of the large amount required.

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