[CONTRIBUTION FROM THE SOUTHERN REGIONAL RESEARCH LABORATORY][1]

The Preparation and Properties of β-Lactyl-α,γ-dipalmitin[2,3]

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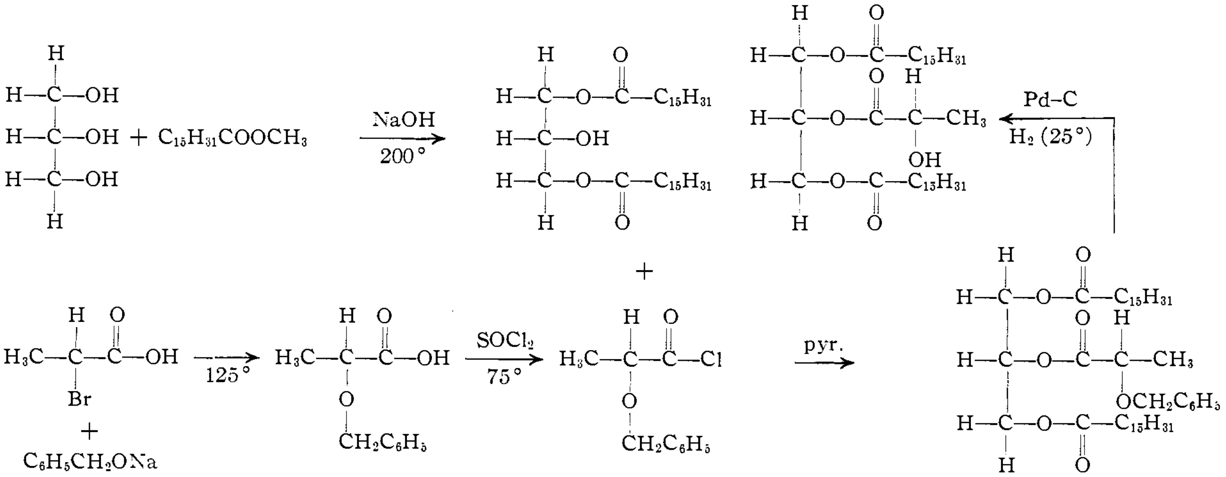
β-Lactyl-α,γ-dipalmitin was prepared by the reaction of α,γ-dipalmitin with the benzyl ether of lactyl chloride and hydrogenolysis of the benzyl group. Ultraviolet spectra to 220 mμ and infrared spectra from 2 to 12μ of benzyllactic acid, the benzyl ether of lactyldipalmitin and of lactyldipalmitin were obtained.

The preparation of a synthetic triglyceride containing a lactyl group in place of one of the long chain acyl groups normally present in fats was undertaken as part of a project on the preparation of various natural and synthetic fats for intravenous administration. Fat emulsions that can be given intravenously would provide an opportunity to overcome the major inadequacy of present parenteral nutrition—that of calories.[4] The solutions presently used, *e.g.*, glucose or protein hydrolysates, do not afford a sufficient number of calories in a reasonable fluid volume. On the other hand, about 2 liters of a 10 to 15% fat emulsion can provide the daily requirement of 1,500 to 3,000 calories. The large amount of emulsifier required to produce and preserve stable emulsions of the fine particle size required (average less than 1 μ with no particles exceeding 4 μ in size) and the lack of suitable emulsifiers which are non-toxic (or non-thermogenic) when administered intravenously have been a serious deterrent to the development of such emulsions. It was thought that a fat containing a hydroxyl group in the fatty acid portion would have a lower interfacial tension against water and it would thus be more easily emulsified and the resultant emulsion would be more stable than one from a triglyceride composed exclusively of long chain fatty acids. For ease of emulsification and utilization in the body it is desired that the fat to be emulsified melt at a low temperature, preferably below 50° since it has been shown that such natural fats are practically completely digested by the normal individual whereas higher melting fats are incompletely absorbed.[5] Further, it was felt that the hydroxylated moiety should preferably be one that readily enters the Krebs cycle. The preparation of lactyldipalmitin was undertaken for these reasons and for subsequent utilization tests.

The preparation of lactic esters of glycerol by direct esterification,[6] by ester interchange,[7] by reaction of glycerol dihalohydrin and sodium lactate[8] and by treating glycerol with O-benzyllactic acid chloride followed by hydrogenolysis[9] have been reported. Attempts to prepare lactyldipalmitin by direct esterification of dipalmitin with lactic acid and by ester interchange of tripalmitin with ethyl lactate led to gross mixtures which could not be purified to produce any portion for which all the analytical data, especially the hydroxyl value and saponification value, corresponded to those calculated for lactyldipalmitin (hydroxyl value 87.5, saponification value 262.5). Reaction of 3-chloro-1,2-dipalmitin with sodium lactate at 160° resulted in a nearly quantitative yield of sodium chloride and α,γ-dipalmitin. However, the following series of reactions led to the desired product.



The characteristic absorption in the ultraviolet region of the benzyl moiety affords a convenient method of analysis for O-benzyllactic acid and O-

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(2) Presented at the Spring Meeting of the American Chemical Society, Kansas City, Missouri, March 24–April 1, 1954.

(3) This investigation was supported in part by funds from the Office of the Surgeon General.

(4) F. G. Stare and R. P. Geyer, *Surg. Gynecol. & Obstet.*, **92**, 246 (1951).

(5) H. J. Deuel, Jr., in "Cottonseed and Cottonseed Products," Interscience Publishers, Inc., New York, N. Y., 1948, p. 780.

(6) J. T. Stearns, B. Makower and P. H. Groggins, *Ind. Eng. Chem.*, **32**, 1335 (1940).

(7) R. H. Lock, U. S. Patent 2,089,127 (August 3, 1937).

(8) G. G. Urquhart, U. S. Patent 2,315,168 (March 30, 1943).

(9) L. Feldmann and H. O. L. Fischer, *Arch. Biochem.*, **14**, 117 (1947).

benzyllactyldipalmitin, and the absence of such characteristic absorption in the spectrum of lactyldipalmitin was very helpful in following the progress of the hydrogenolysis and the purification of the lactyldipalmitin. Infrared spectra show the presence of free hydroxyl by a sharp band at 2.7 μ, attributed to stretching of free OH, in the spectrum of lactyldipalmitin and of dipalmitin but absent from the spectrum of O-benzyllactyldipalmitin and O-benzyllactic acid. The latter shows only the bonded OH of the COOH group revealed by a weak inflection at 3.2 μ and a broadening of the 3.4 μ CH stretching band. It is noteworthy that lactyldipalmitin, although a triglyceride, also shows absorption at 9.6 μ, generally considered characteristic of diglycerides. The band at 2.8 μ, attributed to a single-bridge dimer of the OH group, present in the spectrum of dipalmitin but absent from that of lactyldipalmitin serves to distinguish the diglyceride from the hydroxy substituted triglyceride. The spectra of dipalmitin and lactyldipalmitin also reveal complete absence of a benzyl moiety by lack of characteristic absorption at 9.8 μ, clearly evident in the spectra of O-benzyllactic acid and O-benzyllactyldipalmitin.

Experimental

Methyl Palmitate.—Commercial palmitic acid (90% palmitic, 4% oleic and 6% stearic) was converted to the methyl ester and fractionally distilled through a four-foot Podbielniak Heligrid column.[10] The heart cut used for the preparation of dipalmitin melted at 30.1–30.3° and had an iodine value of 0.12, indicating the presence of about 0.1% oleic acid.

Dipalmitin.—α,γ-Dipalmitin was prepared from glycerol and methyl palmitate[11] and was purified by three crystallizations from 60% isopropyl alcohol[12] followed by four crystallizations from commercial hexane (Skellysolve B).[10] The dipalmitin thus obtained had a m.p. 72–72.5°; 3.01% OH (calcd. 2.98%); infrared spectrum ($CHCl_3$); λ_{max} 2.73, 2.83, 9.61 μ.

O-Benzyllactic Acid and Chloride.—α-Bromopropionic acid (Eastman Kodak Co.)[10] was converted to sodium O-benzyllactate by the method of Feldmann and Fischer.[9] A better yield of crystalline O-benzyllactic acid was obtained by extraction than by the distillation procedure used by Feldmann and Fischer to remove the excess benzyl alcohol. Precipitated sodium bromide was removed from the reaction mixture by filtering or centrifuging and the clear benzyl alcohol solution of sodium O-benzyllactate was extracted four times with water. For the last water extraction ether was added to the alcohol layer to facilitate separation. The combined aqueous extracts were washed with ether acidified with concd. H_2SO_4 and extracted three times with ether. The combined ether extracts were water-washed and dried. After removal of the ether, the O-benzyllactic acid crystallized spontaneously on standing. On filtering, crystalline O-benzyllactic acid, m.p. 39–42°, was obtained in 50–55% yield. Working up the filtrate resulted in isolation of additional crystalline acid (20–25%). Recrystallized from petroleum ether the acid melted at 41–42.5°; ultraviolet spectrum (isoöctane), λ_{max} 252, 258 (ε 196), 264 mμ; infrared spectrum ($CHCl_3$), λ_{max} 2.89, 9.81–9.85 μ. Crystalline O-benzyllactic acid was converted readily to the acid chloride by means of thionyl chloride.[9] On distillation, the acid chloride, $n^{26}D$ 1.5069, was obtained in substantially quantitative yield.

O-Benzyllactyldipalmitin.—In a typical experiment a solution of 50 g. of dipalmitin (0.87 mole) in 160 ml. of dry chloroform was added slowly with continuous stirring to a cooled (−10°) solution of 17.7 g. of O-benzyllactyl chloride (0.89 mole) in 25 ml. of dry chloroform and 15 ml. of freshly distilled pyridine. The solution was maintained at −5 to 0° during the addition. The solution was then permitted to warm up to room temperature (25°) and to stand in the dark for three days. It was then diluted with 440 ml. of ether and washed successively with cold water, 0.5 N H_2SO_4, 5% $KHCO_3$, and again with water and dried with Na_2SO_4. Removal of the solvents under reduced pressure at about 40° left a pasty residue which contained about 90% O-benzyllactyldipalmitin as judged by ultraviolet analysis. This was recrystallized from hexane (12 ml./g.) taking crops at 0° (chiefly dipalmitin, m.p. 70–72°) and at −25°. On recrystallization, O-benzyllactyldipalmitin melting at 25–27° which was estimated to contain 99% of the benzyl compound, as judged by ultraviolet analysis, was obtained in about 70% yield; ultraviolet spectrum (isoöctane), λ_{max} 252, 258 (ε 199) 264 mμ; infrared spectrum ($CHCl_3$), λ_{max} 9.80 μ.

Anal. Calcd. for $C_{45}H_{78}O_7$: C, 73.93; H, 10.75. Found: C, 73.20, 73.08; H, 10.65, 10.54.

β-Lactyl-α,γ-dipalmitin.—1.000 g. of O-benzyllactyldipalmitin was dissolved in 50 ml. of glacial acetic acid and hydrogenated at room temperature in the presence of 0.5 g. of 10% Pd–C in a quantitative hydrogenator. The theoretical amount of hydrogen was taken up after 90 minutes. The hydrogenation was continued for an additional 45 minutes during which time 4% more hydrogen was taken up. The lactyldipalmitin was recovered by filtering off the catalyst, diluting the solution with 10 volumes of cold water, and filtering off the precipitated product at 0°. The dried crude product obtained in substantially quantitative yield melted at 47–48.5° and its ultraviolet absorption spectrum showed complete absence of characteristic aromatic absorption. When recrystallized from absolute alcohol (40 ml./g.) the melting point was raised to 49.7–50.5°; infrared spectrum ($CHCl_3$), λ_{max} 2.73, 9.60 μ.

Anal. Calcd. for $C_{38}H_{72}O_7$: C, 71.20; H, 11.32; OH, 2.65. Found: C, 71.38, 71.40; H, 11.32, 11.22; OH, 2.67.

Larger quantities of O-benzyllactyldipalmitin were hydrogenated in a Burgess–Parr apparatus[10] using an equal volume of acetic acid and about 5% of 10% Pd–C at 40–50° with substantially the same yields of lactyldipalmitin although the time required to complete the hydrogenation was extended to 20 to 30 hours. O-Benzyllactyldipalmitin is very difficult to remove from lactyldipalmitin by crystallization. In one experiment in which about 4% O-benzyllactyldipalmitin was found after hydrogenation two recrystallizations from alcohol, each resulting in 10 to 20% loss, only resulted in decreasing the O-benzyllactyldipalmitin content to 2%, as judged by ultraviolet analysis. However, complete removal of benzyl groups was effected readily by submitting the product to rehydrogenation.

The surface tension and interfacial tension against water of lactyldipalmitin measured at 75° by the method of Ferguson and Kennedy[13] were found to be 18.9 and 14.7 dynes per cm., respectively. These are somewhat lower than the values for the surface tension and interfacial tension of many purified long-chain triglycerides, *e.g.*, for cottonseed oil at 30°. Halpern[14] reported a surface tension of 34.7 dynes per cm. and for interfacial tension, values of 20.8 to 22.4 dynes per cm. at the same temperature have been reported.[15]

Lactyldipalmitin is saponified fairly rapidly at room temperature by 0.01 N alcoholic alkali (about 25% of the lactic acid is hydrolyzed off in an hour) and by 0.02 N aqueous alkali (about 20% in two hours). However, it is hydrolyzed quite slowly by water; stirring a fine suspension in water for a week at room temperature resulted in the hydrolysis of less than 1%.

Acknowledgment.—The authors are grateful to Mrs. Elsie F. Dupre for the infrared spectra, to Donald Mitcham for the ultraviolet spectra, to Robert T. O'Connor for their interpretation, to Mrs. R. Benerito and W. S. Singleton for the surface tension and interfacial tension measurements,

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[10] Mention of names of firms or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

[11] R. O. Feuge and A. E. Bailey, *Oil and Soap*, **23**, 259 (1946).

[12] R. O. Feuge and A. T. Gros, *J. Am. Oil Chemists' Soc.*, **27**, 117 (1950).

[13] A. Ferguson and S. J. Kennedy, *Proc. Phys. Soc.*, **44**, 511 (1932).

[14] A. Halpern, *J. Phys. and Colloid Chem.*, **53**, 895 (1949).

[15] J. R. Pound, *J. Phys. Chem.*, **30**, 791 (1926).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

A Study of the Schönberg Rearrangement of Diaryl Thioncarbonates to Diaryl Thiolcarbonates[1]

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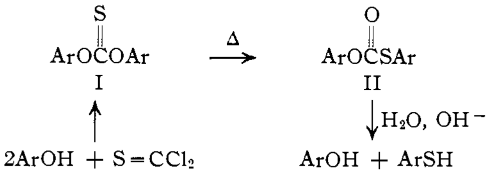
A study of twelve examples of the Schönberg rearrangement of diaryl thioncarbonates to diaryl thiolcarbonates has shown that the reaction is favored by electron-withdrawing groups in the *ortho* and *para* positions. It is suggested that the reaction involves a cyclic transition state, with a nucleophilic attack of the thion sulfur on the aromatic nucleus. The similarity of this rearrangement to the Smiles, Chapman and Stevens rearrangements, and to reactions involving a shift from oxygen to sulfur, is discussed.

The rearrangement of diaryl thioncarbonates I to diaryl thiolcarbonates II which was discovered by Schönberg[2] offers a way of converting phenols to thiophenols, and it appeared to be of synthetic value in obtaining some substituted thiophenols which were needed in studies on the cleavage of sulfides by acids.[3] In addition, the reaction offers some interesting problems from the mechanistic side. The present paper reports the preparation of a number of symmetrical and unsymmetrical diaryl thioncarbonates, and a study of their rearrangement to the thiolcarbonates. From the observations reported it is possible to establish some features of the mechanism of the reaction.



$$\begin{array}{ccc} \mathrm{ArO}\overset{\mathrm{S}}{\overset{\|}{\mathrm{C}}}\mathrm{OAr} & \xrightarrow{\Delta} & \mathrm{ArO}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{SAr} \\ \mathrm{I} & & \mathrm{II} \\ \uparrow & & \downarrow{\scriptstyle \mathrm{H_2O,\ OH^-}} \\ 2\mathrm{ArOH} + \mathrm{S{=}CCl_2} & & \mathrm{ArOH} + \mathrm{ArSH} \end{array}$$

The symmetrical thioncarbonates were prepared by the action of thiophosgene on the phenols in two stages,[4] or, more conveniently, by treatment of a benzene solution of two moles of the phenol and one mole of thiophosgene with dry pyridine.[2] The compounds synthesized are listed in Table I, and the yields of pure material ranged from 20 to 28%.

TABLE I

DIARYL THIONCARBONATES, ArOC(=S)OAr

Ar, phenyl	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen % Calcd.	Hydrogen % Found
2,6-Dimethyl-	111–112	$C_{17}H_{18}O_2S$	71.65	71.37	6.34	6.18
2,4-Dimethyl-	76.5–77.5	$C_{17}H_{18}O_2S$	71.65	71.51	6.34	6.24
4-Chloro-	158–158.5	$C_{13}H_8Cl_2O_2S$	52.23	52.26	2.69	2.82
2-Chloro-	84–84.5	$C_{13}H_8Cl_2O_2S$	52.23	52.16	2.69	2.95
2,4-Dichloro-	94–94.5	$C_{13}H_6Cl_4O_2S$	42.16	42.43	1.72	1.97
4-Bromo-	174–175	$C_{13}H_8Br_2O_2S$	40.25	40.20	2.38	2.22
4-Methoxy-	161–162	$C_{15}H_{14}O_4S$	62.05	61.75	4.92	5.16
2-Methoxy-	68.5–69.5	$C_{15}H_{14}O_4S$	62.05	62.44	4.92	5.19
4-Nitro-	196–197	$C_{13}H_8N_2O_6S$	48.73	48.60	2.55	2.74

The rearrangement reactions were carried out for the most part by heating without solvent to temperatures in the 275–300° range. The product was isolated and characterized; its structure was checked by alkaline hydrolysis, which formed the phenol and the thiophenol. Oxidation of the hydrolysis mixture with hydrogen peroxide converted the thiophenol to the neutral diaryl disulfide, which was found in each case to have a m.p. agreeing with that previously reported.

The bis-(4-nitrophenyl) thioncarbonate decomposed violently when heated to 275–285°; it rearranged smoothly, however, at 252°, in a test-tube heated by refluxing diphenyl ether vapors. The bis-(4-methoxyphenyl) thioncarbonate was recovered virtually unchanged after heating to 300°: it was unchanged by refluxing in diphenyl ether solution for 6 hr., either alone, or in the presence of catalytic amounts of isoquinoline. The 2,4-dichlorothion compound was recovered unchanged after refluxing for 2 hr. in benzyl chloride solution.

From these and numerous other experiments relating time, temperature of heating and yield, it is possible to conclude that the effect of substituents in increasing the rate of the rearrangement is indicated by the series: 4-nitro > 2,4-dichloro > 2- and 4-chloro > 4-bromo > 2,4- and 2,6-dimethyl > 2- and 4-methoxy.

The effect of electron-withdrawing groups in promoting the rearrangement, which is indicated above, was confirmed by a study of the unsymmetrical thioncarbonates listed in Table III. The 2,6-dimethylphenyl 2′-nitrophenyl compound decomposed after standing some time at room temperature; the phenyl 4-chlorophenyl and phenyl 4-nitrophenyl compounds were decomposed by heating at 285°. Heating these two at 240°, however, gave the thiol compounds, in which the substituted phenyl groups had migrated to the sulfur in each case. The structure of the rearranged compounds was demonstrated by alkaline hydrolysis, oxidation and identification of the disulfide.

The rearrangement of the unsymmetrical thion compound, phenyl 2-naphthyl thioncarbonate (III), was examined in more detail. Heating this compound at 275° for 45 minutes yielded 44% of starting material, 12% of bis-(2-naphthyl) thioncarbonate (IV), no bis-(2-naphthyl) thiolcarbonate (V)

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[1] This research was supported in part by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command. Article not copyrighted.

[2] (a) A. Schönberg and L. Vargha, *Ber.*, **63**, 178 (1930); (b) A. Schönberg, L. Vargha and W. Paul, *Ann.*, **483**, 107 (1930).

[3] *Cf.* D. P. Harnish and D. S. Tarbell, THIS JOURNAL, **70**, 4123 (1948); **74**, 1862 (1952); D. S. Tarbell and J. C. Petropoulos, *ibid.*, **74**, 244 (1952).

[4] H. Rivier, *Bull. soc. chim. France*, [3] **35**, 837 (1906).