base. After evaporating the solution to dryness, the organic material was taken up in chloroform and filtered from inorganic salts. The filtrate was again taken to dryness *in vacuo* leaving 208 mg. of residue. Crystallization from ether gave fine needles of methyl 18-desoxyreserpate (XLIV), 175 mg., m.p. 227–229°, $[\alpha]_D$ −39° (chloroform).

Anal. Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59. Found: C, 69.06; H, 7.66.

Attempted Reaction of Sodium Acetate on Methyl Reserpate Bromide.[5]—One gram of methyl reserpate bromide was refluxed with 4 g. of sodium acetate in 30 ml. of ethanol–water (9:1) for four days. The solution was concentrated to a small volume *in vacuo*, diluted with water, and the solid product filtered. Crystallization from methanol yielded 0.6 g. of methyl reserpate bromide, m.p. 210–215°. Its identity was established by the usual criteria.

Action of Alkali on Methyl Reserpate Bromide.[5] (a).—Methyl reserpate bromide (300 mg.) was refluxed in a mixture of 10 ml. of methanol and 3 ml. of 1 *N* aqueous sodium hydroxide for 3 hours. The methanol was distilled *in vacuo* to a volume of a few ml. This was diluted with 10 ml. of water and neutralized with acetic acid. The amino acid which precipitated was suspended in ethanol and methylated with ethereal diazomethane. The reaction mixture was worked up in the usual way and the residue recrystallized from methanol. Starting material (0.2 g.) of m.p. 210–215° was obtained. Its identity was established by the usual criteria.

(b).—The above reaction was repeated except that the refluxing was continued for 18 hours. It was worked up in the same manner as described above. The crude methylated residue was recrystallized from methanol to yield 0.10 g. of methyl reserpate bromide. The mother liquor from this step (methyl reserpate is very soluble in methanol) was concentrated to dryness and treated with 2 ml. of pyridine and 2 ml. of acetic anhydride at room temperature overnight. This was distilled to a small volume, treated with ice-water, ammonia and extracted with chloroform. Recrystallization of the residue remaining after evaporation of the chloroform to dryness gave 40 mg. of methyl reserpate acetate, m.p. 288–290°. Its identity was established by the usual criteria.

Quaternization of Methyl Reserpate Iodide.[5]—Methyl reserpate iodide (100 mg.) was refluxed in 1 ml. of dimethylformamide for 15 min. The reaction mixture was diluted with 5 ml. of water and the solid separating was recrystallized from ethanol to yield 25 mg. of the iodide of XLI. The identity of the sample was established by the usual criteria.

3,4,5,6-Tetradehydroreserpine Perchlorate (XLVIa).[6] A mixture of 1.80 g. of reserpine (XXXIVc), 5.40 g. of maleic acid and 400 mg. of palladium black in 200 ml. of 50% aqueous methanol was refluxed for 72 hours. After filtration of the catalyst the solution was concentrated to 100 ml. on the steam-bath, treated with 5.0 ml. of perchloric acid and cooled for 18 hours. The resulting precipitate was washed thoroughly with boiling ether, and the residue suspended in 100 ml. of cold methanol and filtered from 450 mg. of unreacted reserpine. Evaporation of the methanol solution left 980 mg. (47%) of crude solid, m.p. 156–180°. Crystallization from methanol–isopropyl alcohol gave yellow plates, m.p. 194–196°; ultraviolet spectrum (EtOH): λ_{max} 265 mμ (log ε 4.37), 295 mμ (log ε 4.05) and 382 mμ (log ε 3.83); $[\alpha]_D$ −124° ($CHCl_3$).

Anal. Calcd. for $C_{33}H_{37}O_{13}N_2Cl\cdot CH_3OH$: C, 55.40; H, 5.61; N, 3.80. Found: C, 55.11; H, 6.02; N, 3.80.

9,10,11,12-Tetrahydro-3,4,5,6-tetradehydrodeserpidine Perchlorate (XLVII). (a)[6].—A mixture of 80 mg. of 3,4,5,6-tetradehydrodeserpidine perchlorate (XLVIb)[2] and 50 mg. of PtO_2 in 75 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure for 27 hours, at which time the hydrogen uptake had become negligible. Filtration of the catalyst and removal of the solvent left a colorless glass, which was taken up in 2 ml. of methanol and treated with 5 ml. of water and a drop of perchloric acid. On cooling for 12 hours, 50 mg. (62%) of a solid, m.p. 184–190°, separated. Crystallization from aqueous methanol gave colorless crystals, m.p. 188–190°; ultraviolet spectrum (EtOH): λ_{max} 250 mμ (log ε 4.17), 270 mμ (log ε 4.10) and 335 mμ (log ε 3.62); $[\alpha]_D$ −39° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{33}O_{12}N_2Cl$: C, 56.59; H, 5.79; N, 4.13. Found: C, 55.90; H, 5.25; N, 4.25.

(b).[6]—A mixture of 400 mg. of 3,4,5,6-tetradehydroreserpine perchlorate (XLVIa) and 150 mg. of PtO_2 in 125 ml. of glacial acetic acid was hydrogenated for 30 hours at room temperature and 45 lb. pressure. The reaction mixture was worked up as above yielding 230 mg. (61%) of product, m.p. 175–185°. Several crystallizations from aqueous methanol gave XLVII, m.p. 188–190°, m.m.p. 188–189° with sample above; identical infrared spectrum (KBr) with that of above sample; ultraviolet spectrum (EtOH): λ_{max} 250 mμ (log ε 4.16), 270 mμ (log ε 4.10) and 335 mμ (log ε 3.61); $[\alpha]_D$ −40° ($CHCl_3$).

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Synthesis of L-α-Lecithins Containing Shorter Chain Fatty Acids. Water-soluble Glycerolphosphatides. I

BY ERICH BAER AND VAIDYANATH MAHADEVAN

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The didecanoyl-, dioctanoyl- and dihexanoyl-L-α-lecithins have been synthesized from the appropriate D-α,β-diglycerides by the procedure of Baer and Kates for the synthesis of the enantiomeric forms of α-lecithins. The required, but unknown, D-α,β-diglycerides of capric, caprylic and caproic acid were prepared by the method of Sowden and Fischer. The water-soluble L-α-(dihexanoyl)-lecithin should prove to be an excellent substrate for chemical and biochemical studies in homogeneous aqueous systems.

In 1950, Baer and Kates reported a general method for the synthesis of enantiomeric α-lecithins,[1] and described in detail the preparation of distearoyl-, dipalmitoyl- and dimyristoyl-L-α-lecithin. The lecithins were obtained by phosphorylation of the appropriate D-α,β-diglyceride with phenylphosphoryl dichloride and pyridine, esterification of the resulting phenylphosphatidyl chloride with choline chloride, isolation of the phenyllecithin as reineckate, conversion of the reineckate to sulfate, and removal of the protective phenyl group by catalytic hydrogenolysis. Two years later, Baer and Maurukas[2] succeeded in simplifying this procedure, by replacing the rather time-consuming separation of the phosphorylation products *via* their reinecke salts with a procedure based on the different solubilities of the phosphorylation products in ethanol, benzene and

(1) E. Baer and M. Kates, THIS JOURNAL, **72**, 942 (1950).

(2) E. Baer and J. Maurukas, *ibid.*, **74**, 158 (1952).

acetone. In the intervening years, the three lecithins have been widely used as substrates in a variety of biological investigations. Their usefulness was somewhat limited, however, by their insolubility in water. Hence, the synthesis of a water-soluble lecithin, giving water-soluble degradation products, seemed highly desirable, as it would allow one to work in homogeneous aqueous systems.[3] One might expect to obtain these by shortening the carbon chain length of the hydrophobic fatty acid substituents, permitting the hydrophilic character of the more polar portion of the molecule to predominate. The point of transition from water-insoluble to water-soluble lecithin not being predictable, the didecanoyl-, dioctanoyl- and dihexanoyl-α-lecithins were prepared. The latter proved to be water-soluble. Thus, apparently the acquisition of a significant solubility in water occurs in the saturated lecithin containing the C-7 fatty acid.

For the synthesis of these lecithins we had at our disposal our original[1] and our modified[2] procedures. Anticipating that the separation of the nitrogenous phosphorylation products would become progressively more difficult with decreasing length of the fatty acid chain, we resorted to our original procedure which effects their separation by means of the reinecke salts. Although this method is more time consuming, it has the advantage of yielding with certainty a pure lecithin. This is of importance when the lecithin is being prepared for the first time. In synthesizing the short-chain α-lecithins preference was given to the stereoisomers possessing the L-configuration,[4] which is that of naturally occurring glycerolphosphatides.[1,5,6] A reaction scheme describing in detail our synthetic procedure will be found in our first report on the synthesis of enantiomeric α-lecithins[1] and should be consulted there. The required starting materials, the D-α,β-diglycerides containing capric, caprylic and caproic acids, had not been described in the literature. They were prepared from D-acetone glycerol by the elegant method of Sowden and Fischer.[7] While the work was in progress, Mathieson and Russell[8] reported the synthesis of D-α,β-didecanoylglycerol by the same method. The authors state, however, that its optical rotation and that of the C_{12}-homolog were too small to permit of accurate determination. Since our diglyceride preparation possessed distinct and measurable optical activities both in substance and in chloroform solution, as did all other known members of this series,[1,7,9,10] we investigated its optical behavior in a series of solvents at concentrations ranging from 5 to 80%, in the hope that

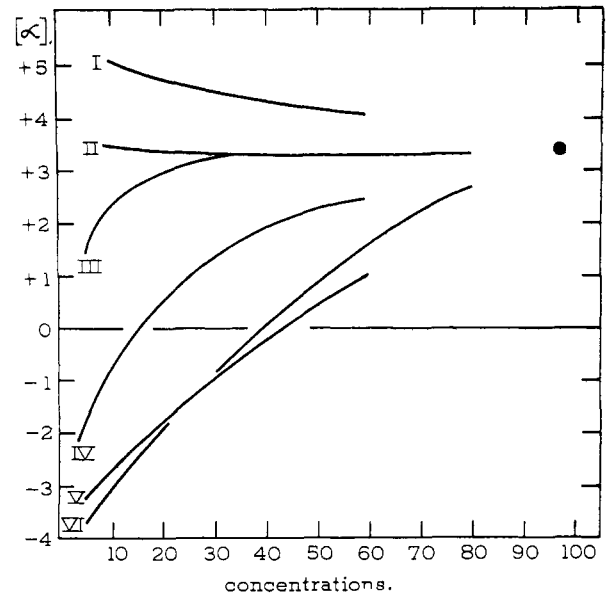

Fig. 1.—Optical activity ([α]D) of D-α,β-(didecanoyl)-glycerol in various solvents as functions of substrate concentration: [α]D of D-α,β-(didecanoyl)-glycerol in substance (supercooled state) (●); acetone (I), dioxane (II), hexane (III), tetrachloromethane (IV), dichloromethane (V) and chloroform (VI); concentration = g. per 100 ml. of solution.

the cause of the disparity in rotations would reveal itself. The measurements (Fig. 1, curves 1–6) show that the solvents fall into two distinct groups, those in which the specific rotation of the diglyceride remains fairly constant over the whole range of concentrations, and those in which it undergoes considerable changes from negative values for low concentrations to positive values for high concentrations. Zero-values were observed at the approximate concentrations of 15% for tetrachloromethane, 40% for chloroform and 43% for dichloromethane. Other members of the homologous series presumably will show similar optical behavior. Possibly Mathieson and Russell determined the optical activity of their diglycerides in one of the chlorinated solvents, and at substrate concentrations that would give zero or near-zero readings.

The L-α-lecithins with caproic, caprylic and capric acid substituents have the molecular rotations of +51.4, +50.9 and +51.0°, respectively. These values agree fairly well with those reported by us for their higher homologs containing myristic (+48.7°), palmitic (+49.5°), stearic (+49.3°)[1] and oleic acid (+49.8°) substituents,[6] and when averaged give a molecular rotation of +50.1° for the L-α-lecithin series containing saturated *n*-fatty acids. This knowledge offers a valuable tool for assessing the stereochemical purity of new members of this series since it provides a constant that permits their specific rotations to be calculated with considerable accuracy (±2%).

The L-α-lecithins with capric, caprylic and caproic acid substituents were found to be highly soluble in methanol and ethanol. This was to be expected, as we had shown that in the saturated α-lecithin series, the solubility in these two solvents

(3) O. A. Roholt and M. Schlamowitz, *Arch. Biochem. Biophys.*, **77**, 510 (1958).

(4) For the guiding principles in the assignment of configuration to asymmetrically substituted glycerides and glycerolphosphatides see E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 475, 491 (1939), and E. Baer and M. Kates, ref. 1.

(5) E. Baer, J. Maurukas and M. Russell, THIS JOURNAL, **74**, 152 (1952).

(6) E. Baer, D. Buchnea and A. G. Newcombe, *ibid.*, **78**, 232 (1956).

(7) J. C. Sowden and H. O. L. Fischer, *ibid.*, **63**, 3244 (1941).

(8) D. W. Mathieson and D. W. Russell, *J. Pharm. and Pharmacol.*, **9**, 251 (1957).

(9) E. Baer and D. Buchnea, *J. Biol. Chem.*, **230**, 447 (1958).

(10) E. Baer and F. Martin, *ibid.*, **193**, 835 (1951).

increases steeply from distearoyl- to dimyristoyl-lecithin.[1] An even sharper increase occurs in the acetone solubility of the members of this series with decreasing chain length of the fatty acid substituents. Lecithins containing stearic, palmitic or myristic acids are practically insoluble in acetone at room temperature[1] (less than 60 mg. per 100 ml. of solvent); those containing fatty acids with eight or less carbon atoms are highly soluble. These unexpected solubilities of the simpler saturated α-lecithins in methanol, ethanol and acetone suggest that lecithins of this type, if they do occur in nature, would have escaped recognition because they would be lost in conventional fractionation procedures.

L-α-(Dihexanoyl)-lecithin promises to become a valuable substrate for biochemical studies because it provides for the first time a chemically pure lecithin that may be investigated in a homogeneous aqueous system.

Experimental

D-α,β-Diglycerides. D-α,β-Didecanoylglycerol Benzyl Ether.—In a three-necked round flask with ground joints and equipped with a mechanical stirrer, dropping funnel and calcium chloride tube were placed 49.0 g. (0.257 mole) of freshly distilled *n*-decanoyl chloride.[11] The flask was immersed in a bath of ice-water, and a solution of 23.0 g. (0.126 mole) of L-α-benzyl glycerol ether[12] and 21.0 g. (0.265 mole) of anhydrous pyridine[13] in 100 ml. of anhydrous benzene was added gradually and with stirring to the acid chloride. When the addition was complete, additional amounts of pyridine (10 ml.) and benzene (30 ml.) were added, and the mixture was kept at 38° for 18 hours. The reaction mixture was then cooled to room temperature, diluted with 250 ml. of anhydrous ether and centrifuged. The precipitate was washed twice with 200 ml. of ether. The combined solutions were washed successively with ice-cold 2 *N* sulfuric acid, water, a saturated sodium bicarbonate solution, and again with water until the wash water was neutral to litmus. The ethereal solution was dried with anhydrous sodium sulfate, and the solvents were distilled off under reduced pressure. The crude material, weighing 59.4 g. (96.1% of theory calculated for benzyl glycerol ether), was purified by low-temperature crystallization from acetone at −50° (10 ml. of acetone per 1 g. of material), and freed of solvent in a high vacuum (0.01 mm.) at a bath temperature of 35–40°. The D-α,β-didecanoylglycerol benzyl ether was recovered in a yield of 90%, $n^{22}D$ 1.4748, d^{20}_4 0.9685, m.p. 7–8°, $[\alpha]^{23}D$ +10.7° in substance, $[\alpha]^{23}D$ +8.2° in ethanol-free chloroform (*c* 10.4), M_D +40.2° in chloroform.

Anal. Calcd. for $C_{30}H_{56}O_5$ (490.7): C, 73.43; H, 10.27. Found: C, 73.55; H, 10.32.

D-α,β-Dioctanoylglycerol benzyl ether was prepared as the C_{10}-homolog. The acylation of 22.7 g. (0.125 mole) of L-α-benzyl glycerol ether with 40.7 g. (0.25 mole) of *n*-octanoyl chloride[11] and 21.0 g. (0.265 mole) of anhydrous pyridine in 100 ml. of benzene, yielded 50.8 g. (93.6% of theory) of crude D-α,β-dioctanoylglycerol benzyl ether. The recrystallization of this material at low temperature (−70°) from anhydrous acetone (10 ml. of solvent per 1 g. of substance), followed by drying in a high vacuum at room temperature gave 46.0 g. (84.8% of theory) of pure D-α,β-dioctanoylglycerol benzyl ether, $n^{23}D$ 1.4745, d^{20}_4 0.9864, $[\alpha]^{20}D$ +11.56°, in substance M_D +50.24°, $[\alpha]^{20}D$ +9.7° in ethanol-free chloroform (*c* 9.3), M_D +40.7° in chloroform.

Anal. Calcd. for $C_{26}H_{42}O_5$ (434.6): C, 71.85; H, 9.74. Found: C, 71.73; H, 9.81.

D-α,β-Dihexanoylglycerol benzyl ether was prepared as described above for the C_{10}-homolog, by acylation of 22.7 g. (0.125 mole) of L-α-benzyl glycerol ether with 33.6 g. (0.250 mole) of *n*-hexanoyl chloride[11] and 20.9 g. (0.265 mole) of anhydrous pyridine. Obtained was 41.1 g. (86.9% of theory) of D-α,β-dihexanoylglycerol benzyl ether ($[\alpha]D$ +10.1° in chloroform). The crude material was purified by dissolving it in 400 ml. of petroleum ether (b.p. 30–60°) and passing the solution through a column of approx. 400 g. of silicic acid[14] at a flow rate of 12 to 15 ml. per minute, washing the column in succession with 3 l. of petroleum ether, and 1 l. of a mixture of petroleum ether (85 parts) and ethyl ether (15 parts), and removing the solvents of the combined eluates under reduced pressure. The residue was taken up in 200 ml. of acetone, the solution was placed overnight in an ice-box, and cleared by centrifugation. On removing the acetone by distillation under reduced pressure, and keeping the liquid residue for several hours in a good vacuum (0.1 mm.) at room temperature, 35.6 g. (75.2% of theory) of D-α,β-dihexanoylglycerol benzyl ether was obtained, $n^{24}D$ 1.4760, d^{20}_4 1.0105, $[\alpha]^{24}D$ +13.46° in substance, M_D +50.9° in substance, $[\alpha]D$ +10.9° in ethanol-free chloroform (*c* 11), M_D +41.2° in chloroform.

Anal. Calcd. for $C_{22}H_{34}O_5$ (378.5): C, 69.80; H, 9.05; sapn. no., 297. Found: C, 69.80; H, 8.84; sapn. no., 300.

D-α,β-Didecanoylglycerol.—A solution of 14.7 g. (0.03 mole) of D-α,β-didecanoylglycerol benzyl ether in 200 ml. of glacial acetic acid, together with 2.5 g. of palladium black[15] was shaken in an all-glass hydrogenation vessel of 1-l. capacity in an atmosphere of pure hydrogen at an initial pressure of approx. 50 cm. of water until the absorption of hydrogen ceased. The hydrogen was swept out with nitrogen, the catalyst was removed by centrifugation and washed with a small amount of acetic acid. The acetic acid solutions were combined, and the acid was distilled off *in vacuo* at a bath temperature of 30–40°. The remaining acid was removed by keeping the residue in a high vacuum (0.01 mm.) at a bath temperature of 30–35° until its weight was constant. The crude product was purified by low temperature crystallization from anhydrous acetone at −30°, using 10 ml. of acetone per 1 g. of diglyceride. The diglyceride was freed of solvents *in vacuo* at room temperature. The recovered diglyceride weighed 10.5 g. (87.2% of theory). At room temperature, it solidified forming clusters of needles, m.p. 29–30°, d^{20}_4 0.9559 (in super-cooled state), $n^{23}D$ 1.4535 (in super-cooled state), $[\alpha]^{21}D$ +3.33° in substance (super-cooled state), M_D +13.3° in substance, $[\alpha]^{22}D$ −2.9° in ethanol-free chloroform (*c* 12), M_D −11.6° in chloroform.

Anal. Calcd. for $C_{23}H_{44}O_5$ (400.6): C, 68.96; H, 11.07. Found: C, 69.22; H, 10.97.

D-α,β-Dioctanoylglycerol was prepared from the corresponding benzyl ether by catalytic hydrogenolysis as described for the C_{10}-homolog; 13.04 g. of D-α,β-dioctanoylglycerol benzyl ether yielded 9.65 g. of crude diglyceride. This material on recrystallization from anhydrous acetone (10 ml. per gram of substance) at −50°, and drying *in vacuo* at 0.1 mm. gave 8.62 g. (83.4% of theory) of pure D-α,β-dioctanoylglycerol, $n^{21.5}D$ 1.4508, d^{20}_4 0.9766, $[\alpha]^{22}D$ +3.48° in substance, M_D +11.9° in substance, $[\alpha]^{22}D$ −3.4° in ethanol-free chloroform (*c* 10), M_D −11.7° in chloroform.

Anal. Calcd. for $C_{19}H_{36}O_5$ (344.5): C, 66.24; H, 10.53. Found: C, 65.95; H, 10.34.

D-α,β-Dihexanoylglycerol was prepared as described for the C_{10}-homolog. The catalytic hydrogenolysis of 11.35 g. (0.03 mole) of D-α,β-dihexanoylglycerol benzyl ether yielded 8.28 g. (95.7% of theory) of D-α,β-dihexanoylglycerol. As the diglyceride could not be recrystallized from acetone at low temperature, it was purified by chromatography on silicic acid. A solution of the diglyceride (8.28 g.) in 80 ml. of petroleum ether (b.p. 30–60°) was poured through a column of approx. 75 cm. length containing 150 g. of silicic acid,[14] and the column was washed with 80 ml. of petroleum ether. The diglyceride was eluted with a mixture of petroleum ether and ethyl ether (4:1, v./v.), the

(11) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 82 (1939).

(12) L-α-Benzyl glycerol ether was prepared from D-acetone glycerol (E. Baer, *Biochem. Preparations*, **2**, 31 (1952)) by the method of J. C. Sowden and H. O. L. Fischer (THIS JOURNAL, **63**, 3244 (1941)) using the modifications introduced by R. J. Howe and T. Malkin (*J. Chem. Soc.*, 2663 (1951)) for the preparation of the corresponding racemic compound.

(13) Pyridine of good commercial grade was boiled under reflux with barium oxide, and distilled under anhydrous conditions.

(14) Silicic acid (Merck, Reagent Grade).

(15) J. Tausz and N. v. Putnoky, *Ber. Deut. chem. Ges.*, **52**, 1573 (1919).

eluate was freed of solvents by distillation under diminished pressure, and the remaining liquid was kept *in vacuo* (0.1 mm.) until its weight was constant. The recovered D-α,β-dihexanoylglycerol weighed 6.04 g. (70.1% of theory), $n^{25}D$ 1.4450, d^{20}_4 1.005, $[\alpha]D$ +3.7° in substance, MD +10.67° in substance, $[\alpha]D$ −4.14° in ethanol-free chloroform (*c* 9), MD −11.9° in chloroform.

Anal. Calcd. for $C_{15}H_{28}O_5$ (288.4): C, 62.48; H, 9.79; sapn. no., 389. Found: C, 62.75; H, 9.94; sapn. no., 393.

L-α-Lecithins. L-α-(Didecanoyl)-lecithin. Didecanoyl-L-α-glycerylphenylphosphorylcholine Reineckate. Phosphorylation.—In a 300-ml. three-necked round flask with ground joints, and equipped with a mechanical stirrer, dropping funnel and calcium chloride tube was placed 6.33 g. (0.03 mole) of monophenylphosphoryl dichloride,[16,17] the flask was surrounded with an ice-bath, and a mixture of 12.0 g. (0.03 mole) of D-α,β-didecanoylglycerol, 3.0 ml. (0.037 mole) of anhydrous pyridine and 15 ml. of ethanol-free chloroform was added dropwise to the vigorously stirred phosphorylating agent in the course of 1 hour. The cold-bath then was removed and the stirring was continued. One hour later, 10 ml. of pyridine was added dropwise over a period of 30 minutes, and followed by 4.6 g. (0.033 mole) of dry choline chloride,[18] 25 ml. of chloroform and an additional 20 ml. of pyridine. The mixture was kept at room temperature (22–25°) with stirring for 18 hours.

Isolation of Didecanoyl-L-α-glycerylphenylphosphorylcholine as the Reineckate.—The reaction mixture then was concentrated under reduced pressure at a bath temperature of 35–40°, and the residue was freed of pyridine as thoroughly as possible in a high vacuum (0.1–0.01 mm.). The residue was extracted with three 100-ml. portions of anhydrous ether, the extracts were combined, the solvent was removed under reduced pressure, and the remaining material was kept in a high vacuum at 30° for 2 hours. It was then dissolved in 100 ml. of 99% ethanol, and the solution was added slowly and with stirring to 300 ml. of a 5% solution of ammonium reineckate[19] in 99% ethanol. The mixture was kept at +6° for 12 hours and separated by centrifugation. The supernatant solution on concentrating under reduced pressure to one-half of its volume and cooling to +6° gave a second crop of reineckate. (The mother liquor, containing the by-product bis-(didecanoyl-L-α-glyceryl)-phosphoric acid phenyl ester, was worked up as described below.) The reineckate precipitates were combined, washed with 99% ethanol, and dried thoroughly *in vacuo* over calcium chloride. The mixture of reineckates was exhaustively extracted with 200-ml. portions of warm (40–50°) ethyl acetate, and the suspensions were separated by centrifugation. The combined extracts were evaporated to dryness under reduced pressure. The residue was redissolved in 200 ml. of ethyl acetate, the solution was cleared by centrifugation and concentrated under reduced pressure to a volume of approximately 20 ml. To the concentrate was added 150 ml. of 95% ethanol, and the mixture was placed in an ice-box (+6°). The reineckate was filtered off, and the filtrate was concentrated under reduced pressure to one-half of its volume. The concentrate on cooling to +6° yielded a second crop of reineckate. The combined crystalline reineckates of didecanoyl-L-α-glycerylphenylphosphorylcholine,[20] after drying *in vacuo* (0.01 mm.) over calcium chloride, weighed 8.6 g. (29.8% of theory), m.p. 143.5–144.0°. This reineckate, as well as those of the C_8- and C_6-homologs, are highly soluble at room temperature in ethyl acetate, acetone or chloroform, sparingly soluble in ethanol and insoluble in ether.

Anal. Calcd. for $[C_{34}H_{61}O_8NP][(NH_3)_2Cr(SCN)_4]$ (962.2): C, 47.48; H, 7.03; N, 10.20; P, 3.22. Found[21]: C, 47.15; H, 7.16; N, 10.15; P, 3.26.

(16) P. Brigl and H. Müller, *Ber. deut. chem. Ges.*, **72**, 2121 (1939).

(17) H. Zenftman and R. McGillivray, *C. A.*, **45**, 9081 (1951); British Patent 651,656.

(18) To obtain choline chloride in a finely divided form, it was precipitated from a vigorously stirred solution in abs. ethanol by the addition of anhydrous ether. The choline chloride was dried *in vacuo* (0.01 mm.) over phosphorus pentoxide at 56°.

(19) The commercial ammonium reineckate was purified before use by recrystallization from hot water.

(20) The reineckates and sulfates of the phenyllecithins should be processed immediately as they may decompose on keeping.

(21) All carbon–hydrogen combustions of the phosphorus-containing compounds were carried out in the presence of vanadium pentoxide.

Didecanoyl-L-α-glycerylphenylphosphorylcholine Sulfate.—To a vigorously stirred solution of 8.6 g. (8.94 mmoles) of the reineckate of didecanoyl-L-α-glycerylphenylphosphorylcholine in 250 ml. of a mixture of chloroform and methanol (1:1) was added simultaneously and at the same rate 140 ml. of ethanol and 140 ml. of a 1.0% aqueous solution (4.48 mmoles) of silver sulfate. After 10 minutes the mixture was separated by centrifugation, the silver reineckate was washed with two 100-ml. portions of the chloroform–ethanol mixture, and the combined solutions were evaporated to dryness under reduced pressure. (Any foaming occurring at this stage was suppressed by the addition of small amounts of ethanol.) The solid material was dissolved in 40 ml. of warm anhydrous acetone, the warm solution was cleared by centrifugation, and then placed in an ice-box (+6°) for 18 hours. The crystalline sulfate was centrifuged down, washed with a small amount of cold acetone, and dried *in vacuo* over calcium chloride. The didecanoyl-L-α-glycerylphenylphosphorylcholine sulfate, weighing 5.3 g., was obtained in a yield of 85.8% of theory.

Anal. Calcd. for $[C_{34}H_{61}O_8NP]_2SO_4$ (1381.7): N, 2.03; P, 4.48. Found: N, 2.06; P, 4.46.

Didecanoyl-L-α-glycerylphosphorylcholine.—A solution of 5.3 g. of didecanoyl-L-α-glycerylphenylphosphorylcholine sulfate in 150 ml. of 99% ethanol, and 1.5 g. of platinum dioxide[22] were placed in an all-glass hydrogenation vessel of 500-ml. capacity, and the mixture was shaken vigorously in an atmosphere of pure hydrogen at a pressure of approximately 50 cm. of water until the uptake of hydrogen ceased (approx. 90 minutes). The hydrogen was swept out with nitrogen, the catalyst was removed by centrifugation, washed with a small amount of ethanol, and to the combined ethanolic solutions was added 50 ml. of water and 4 g. of finely powdered barium carbonate. The mixture was vigorously shaken for 0.5 hour and then separated by centrifugation. To the decanted supernatant solution were added 4 g. each of the Amberlites IRC-50 (H) and IR-4B,[23] and the mixture was shaken for 30 minutes. The mixture of Amberlites was removed by centrifugation and washed with ethanol. The solutions were combined, and alcohol and water were distilled off under reduced pressure at a bath temperature of 35–40°. The residue, a glass-like material, was dissolved in a small volume of warm anhydrous acetone, the solution was cleared by centrifugation, and placed in an ice-box. After 16 hours the crystalline material was centrifuged down, washed with a small volume of ice-cold acetone, and dried *in vacuo* (0.01 mm.) over calcium chloride. The L-α-(didecanoyl)-lecithin weighed 3.98 g. (88.9% of theory), $[\alpha]^{22}D$ +8.75° in a mixture of chloroform and methanol (1:1) (*c* 4.6), MD +51.0° in chloroform–methanol. The C_{10}-lecithin at room temperature is highly soluble in ethanol, methanol, chloroform, fairly soluble in acetone, insoluble in ether, and readily forms emulsions with water.

Anal. Calcd. for $C_{28}H_{58}O_9NP$ (583.7): C, 57.61; H, 10.02; N, 2.40; P, 5.31. Found: C, 57.01; H, 10.03; N, 2.41; P, 5.29.

L-α-(Didecanoyl)-lecithin Cadmium Chloride Compound.—To a solution of 0.34 g. of L-α-(didecanoyl)-lecithin in 10 ml. of 99% ethanol was added with stirring an ethanolic solution of cadmium chloride that had been prepared by dissolving 0.60 g. of cadmium chloride (2.5 moles of H_2O) in 0.3 ml. of water and adding 9.5 ml. of 99% ethanol. After 30 minutes, the reaction mixture was separated by centrifugation, the precipitate was washed with two 10-ml. portions of 99% ethanol, followed by ether, and dried *in vacuo*. The cadmium chloride compound weighed 0.40 g. (80.1% of theory).

Anal. Calcd. for $[C_{28}H_{58}O_9NP]_2[CdCl_2]_3$ (1717.4): N, 1.63; P, 3.61. Found: N, 1.60; P, 3.65.

L-α-(Dioctanoyl)-lecithin. Dioctanoyl-L-α-glycerylphenylphosphorylcholine Reineckate.—The phosphorylation of D-α,β-dioctanoylglycerol (10.33 g., 0.03 mole) with phenylphosphoryl dichloride (6.33 g., 0.03 mole) and pyridine (2.92 g., 0.037 mole); the esterification of the phosphorylation

(22) The catalyst was prepared as described in "Organic Syntheses," Coll. Vol. I, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 463, with the exception that the sodium nitrate was replaced by an equimolecular amount of potassium nitrate (A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 952 (1934)).

(23) Both Amberlites before being used were washed thoroughly with ethanol to remove all colored material.

product, dioctanoyl L-α-glycerylphenylphosphoryl chloride, with choline chloride (4.6 g., 0.033 mole); and the isolation of the phenyllecithin as reineckate was carried out as described for the C_{10}-homolog. The reineckate of dioctanoyl-L-α-glycerylphenylphosphorylcholine was obtained in a yield of 40.5% of theory (11.0 g.), m.p. 134–135°.

Anal. Calcd. for $[C_{30}H_{53}O_8NP][(NH_3)_2Cr(SCN)_4]$ (905.1): C, 45.11; H, 6.57; N, 10.83; P, 3.42. Found: C, 44.72; H, 6.54; N, 10.90; P, 3.38.

Dioctanoyl-L-α-glycerylphenylphosphorylcholine Sulfate.—The conversion of dioctanoyl L-α-glycerylphenylphosphorylcholine reineckate to the corresponding sulfate was effected as described for the C_{10}-homolog; 11.0 g. of the reineckate yielded 6.8 g. of crude sulfate which, on recrystallization from 25 ml. of anhydrous acetone at −10°, gave 6.54 g. (84.8% of theory) of pure dioctanoyl-L-α-glycerylphenylphosphorylcholine sulfate.

Anal. Calcd. for $[C_{30}H_{53}O_8NP]_2SO_4$ (1269.5): N, 2.21; P, 4.88. Found: N, 2.20; P, 4.88.

Dioctanoyl-L-α-glycerylphosphorylcholine was prepared from the corresponding phenyllecithin sulfate by catalytic hydrogenolysis as described for the C_{10}-homolog; 6.54 g. of dioctanoyl-L-α-glycerylphenylphosphorylcholine sulfate gave 4.72 g. (86.8% of theory) of L-α-(dioctanoyl)-lecithin. It was recrystallized from anhydrous acetone (7–8 ml. of solvent per 1 g. of substance) at −15°, and was thoroughly dried *in vacuo* (0.01 mm.) over calcium chloride; recovery 4.19 g. (88.7%) of lecithin, $[\alpha]^{23}D$ +9.65° in a mixture of chloroform and methanol (1:1, v./v.), M_D +50.9° in chloroform–methanol. The fairly hygroscopic dioctanoyllecithin was found to be very soluble at room temperature in ethanol, methanol, chloroform or acetone, and insoluble in anhydrous ether.

Anal. Calcd. for $C_{24}H_{50}O_9NP$ (527.6): C, 54.63; H, 9.55; N, 2.65; P, 5.87. Found[24]: C, 54.76; H, 9.85; N, 2.60; P, 5.82.

L-α-(Dihexanoyl)-lecithin. Dihexanoyl-L-α-glycerylphenylphosphorylcholine Reineckate.—The phosphorylation of D-α,β-dihexanoylglycerol (17.30 g., 0.06 mole) with phenylphosphoryl dichloride (12.66 g., 0.06 mole) and pyridine (5.84 g., 0.074 mole), the esterification of dihexanoyl-L-α-glycerylphenylphosphoryl chloride with choline chloride (9.2 g., 0.066 mole), and the isolation of the phenyllecithin as reineckate was carried out as described for the C_{10}-homolog. The reineckate of L-α-glycerylphenylphosphorylcholine was obtained in a yield of 35% of theory (17.82 g.), m.p. 130–131°.

Anal. Calcd. for $[C_{26}H_{45}O_8NP][(NH_3)_2Cr(SCN)_4]$ (849): C, 42.44; H, 6.06; N, 11.56; P, 3.65. Found: C, 42.26; H, 6.07; N, 11.70; P, 3.62.

Dihexanoyl-L-α-glycerylphenylphosphorylcholine Sulfate.—The conversion of dihexanoyl-L-glycerylphenylphosphorylcholine reineckate (17.8 g., 21 mmoles) to sulfate was carried out as described for the corresponding C_{10}-homolog. The sulfate was purified by dissolving it in chloroform or ethanol, clearing the solution by centrifugation, and removing the solvent by distillation *in vacuo*. The dry dihexanoyl-L-α-glycerylphenylphosphorylcholine sulfate weighed 10.2 g. (82.6% of theory). It is readily soluble at room temperature in ethanol, acetone, chloroform or water.

Anal. Calcd. for $[C_{26}H_{45}O_8NP]_2SO_4$ (1157): N, 2.42; P, 5.35. Found: N, 2.51; P, 5.21.

(24) The lecithins containing caprylic and caproic acids are hygroscopic. All weighings were carried out under anhydrous conditions.

Dihexanoyl-L-α-glycerylphosphorylcholine.—The lecithin was prepared by catalytic hydrogenolysis of dihexanoyl-L-α-glycerylphenylphosphorylcholine sulfate (10.2 g.) as described for the C_{10}-homolog. The aqueous ethanolic solution of the lecithin was freed of the Amberlites by centrifugation, and the solution was evaporated to dryness under reduced pressure at a bath temperature of 35–40°. The residue was dissolved in 100 ml. of acetone, the solution was cleared by centrifugation, and the acetone was distilled off under reduced pressure. The remaining substance was dried thoroughly *in vacuo* (0.01 mm.) at 56° (boiling acetone) over calcium chloride. The strongly hygroscopic L-α-(dihexanoyl)-lecithin, a white powdery material which on exposure to air changed rapidly to a wax-like material, weighed 5.94 g. (71.5% of theory). It was found to be highly soluble at room temperature in ethanol, methanol, acetone, chloroform or water, and insoluble in anhydrous ether; $[\alpha]^{24}D$ +11.0° (*c* 4.9), $[\alpha]^{25}D$ +10.9° (*c* 9.5), both rotations in ethanol-free chloroform; M_D +51.4° in chloroform, $[\alpha]D$ +10.9° in water (*c* 4.6).

Anal. Calcd. for $C_{20}H_{42}O_9NP$ (471.5): C, 50.94; H, 8.98; N, 2.97; P, 6.57. Found: C, 51.27; H, 8.90; N, 3.05, 2.92; P, 6.50, 6.60.

L-α-(Dihexanoyl)-lecithin cadmium chloride compound was prepared as described for the C_{10}-homolog; 0.40 g. of L-α-(dihexanoyl)-lecithin gave 0.62 g. (98.0% of theory) of the corresponding cadmium chloride compound.

Anal. Calcd. for $[C_{20}H_{42}O_9NP]_2[CdCl_2]_3$ (1493): N, 1.88; P, 4.15. Found: N, 1.82; P, 4.10.

By-products in the Synthesis of the Didecanoyl- and Dioctanoyl-L-α-lecithins. Tetradecanoyl Bis-(L-α-glyceryl)-phosphoric Acid Phenyl Ester.—The alcoholic mother liquor, which remained after the removal of both crops of didecanoyl-L-α-glycerylphenylphosphorylcholine reineckate, was brought to dryness under reduced pressure, the residue was freed of alcohol *in vacuo* over calcium chloride, and the solid material was extracted with three 70-ml. portions of ether. The combined ether extracts were washed several times with water, dried with anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was dissolved in 20 ml. of 99% ethanol, and the solution was placed in an ice-box (+6°) for crystallization. The white, crystalline material was collected with suction on a Buchner funnel, washed with a small amount of ice-cold 99% ethanol, and recrystallized once more in the same manner. The recovered tetradecanoyl bis-(L-α-glyceryl)-phosphoric acid phenyl ester, after drying *in vacuo* over calcium chloride, weighed 3.8 g., m.p. 43–44°, $[\alpha]^{24}D$ +6.0° in benzene (*c* 4), M_D +56.3° in benzene.

Anal. Calcd. for $C_{52}H_{91}O_{12}P$ (939.2): C, 66.49; H, 9.77; P, 3.30. Found: C, 66.38; H, 9.44; P, 3.32.

Tetraoctanoyl-bis-(L-α-glyceryl)-phosphoric Acid Phenyl Ester.—The filtrate from dioctanoyl-L-α-glycerylphenylphosphorylcholine reineckate on working up as described for the C_{10}-homolog gave 2.3 g. of tetraoctanoyl-bis-(L-α-glyceryl)-phosphoric acid phenyl ester, m.p. 23–24°, $[\alpha]D$ +6.4° in benzene (*c* 5), M_D +53.0° in benzene.

Anal. Calcd. for $C_{44}H_{75}O_{12}P$ (827): C, 63.89; H, 9.14; P, 3.75. Found: C, 63.27, H, 9.06; P, 3.80.

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