TABLE III

2-HYDROXY-3-ALKYL-1,4-NAPHTHOQUINONES BY SYNTHESIS

No.	Side chain	Method	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	$-(CH_2)_8CO_2CH_3$	Acid (Paper X), CH_3OH, BF_3-etherate	86–87	$C_{20}H_{24}O_5$	69.75	69.65	7.02	6.93
2	$-(CH_2)_7CO_2H$	Hooker oxid. (71%)	128–129	$C_{18}H_{20}O_5$	68.34	68.63	6.37	6.34
3	Methyl ester		89.5–90.5	$C_{19}H_{22}O_5$	69.07	68.97	6.71	6.77
4	Hydroq. triacetate		145–146	$C_{24}H_{28}O_8$	64.85	65.01	6.35	6.49
5	$-(CH_2)_6CO_2H$	Hooker oxid. (89%)	131–132	$C_{17}H_{18}O_5$	67.64	67.48	6.00	5.86
6	Methyl ester		91–92	$C_{18}H_{20}O_5$	68.34	68.44	6.37	6.35
7	Amide	Acid + $(COCl)_2$; NH_4OH-dioxane (87%)	192–193.5	$C_{17}H_{19}O_4N$	67.76	67.60	6.36	6.70
8	$-(CH_2)_5CO_2H$	Hooker oxid. (84%)	120–121	$C_{16}H_{16}O_5$	66.66	66.81	5.60	5.79
9	Methyl ester	See Table I	94.5–95.5	$C_{17}H_{18}O_5$	67.64	67.70	6.00	6.06
10	$-(CH_2)_4CO_2CH_3$	BF_3-esterification of acid (Paper X)	100–101	$C_{16}H_{16}O_5$	66.42	66.82	5.58	5.66
11	$-(CH_2)_3CO_2H$	Hooker oxid. (87%)	145–146.5	$C_{14}H_{12}O_5$	64.61	64.92	4.65	4.76
12	Methyl ester	See Table I	131–132					
13	$-(CH_2)_2CO_2H$	Hooker oxid. (71%); see also Paper X	195–196					
14	Methyl ester		133–134					
15	$-(CH_2)_7C(OH)(CH_3)_2$	Hooker oxid. of M-2231 (70%)	84–85	$C_{20}H_{26}O_4$	72.70	72.51[a]	7.93	7.88[a]
16	$-(CH_2)_6C(OH)(CH_3)_2$	Hooker oxid. of No. 15 (diff. to cryst.)	83–84	$C_{19}H_{24}O_4$	72.12	72.39	7.65	7.98
17	$-(CH_2)_8COCH_3$	Grig. react. on nitrile	93–95	$C_{20}H_{24}O_4$	73.15	73.34	7.54	7.41
18	$-(CH_2)_6COCH_2CH_2CH_3$	Red acet. of No. 7; Grig. react.	95–96	$C_{20}H_{24}O_4$	73.15	73.35	7.54	7.41
19	$-(CH_2)_4COC_6H_5$	Acetylated acid + $SOCl_2$; C_6H_6 + $AlCl_3$	116–117					
20	Acetate	Ac_2O-BF_3 (see Table I)	136.5–137.5					

[a] Analysis kindly carried out by E. F. Shelberg and Jane Morris of the Abbott Laboratories.

Summary

Chromic anhydride oxidation of 2-acetoxy-1,4-naphthoquinones substituted in the 3-position by various alkyl, aralkyl, cycloalkyl and cycloalkyl-alkyl groups results in an attack of the side chain with the production of tertiary alcohols, ketones, acids and keto acids.

Oxidation proceeds much faster and in higher yield when a glacial acetic acid solution of the substance to be oxidized is agitated with solid chromic anhydride than when the oxide is brought into solution with the use of 10% of water.

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[CONTRIBUTION FROM WESTERN REGIONAL RESEARCH LABORATORY[1]]

Dimyristo- and Eruco-stearo-cephalin

BY I. R. HUNTER, R. L. ROBERTS AND E. B. KESTER

Prior investigations at the Western Regional Research Laboratory on the storage of egg powders revealed the fact that the alcohol-insoluble portion, or cephalin-containing fraction, of the phospholipids present underwent progressive degradative changes concurrently with loss in quality of the egg material. Repeated attempts were made to obtain fresh egg cephalin in pure form to permit a study of its autoxidation in absence of non-phosphatidic matter, but without success. Attention was therefore turned to the synthesis of one or more compounds having the cephalin structure. It was particularly desired to obtain a cephalin with at least one point of unsaturation, on the assumption that oxidative deterioration is initiated at a methylene group adjacent to a double bond in one of the fatty acid groups present.

The synthesis of cephalin has been described in a number of reports,[2] but in these publications the products were not sufficiently characterized to validate the procedures used. A recent synthesis by Rose[3] which yielded a well-defined compound,

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

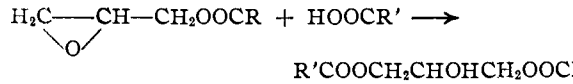
(2) Grün and Limpacher, *Ber.*, **60B**, 151 (1927); Kabashima, *ibid.*, **71**, 76, 1071 (1938); Kabashima and Bunsuke, *Proc. Imp. Acad. Tokyo*, **8**, 492 (1932); *C. A.*, **27**, 1634 (1933).

(3) Rose, THIS JOURNAL, **69**, 1384 (1947).

was used in the current investigation, with certain modifications, for the preparation of α,γ-dimyristo-cephalin and α-eruco-γ-stearo-cephalin. In this synthesis, a so-called "β-cephalin" is formed by a series of reactions on α,γ-diglycerides.

Most preparations of either simple or mixed diglycerides yield the α,γ-form exclusively, even when some of the α,β-form might be anticipated. Only in special instances, and with the use of precautionary measures, is it possible to prepare α,β-diglycerides (that is, to prevent shifting of an acyl group from the β- to the γ-position).

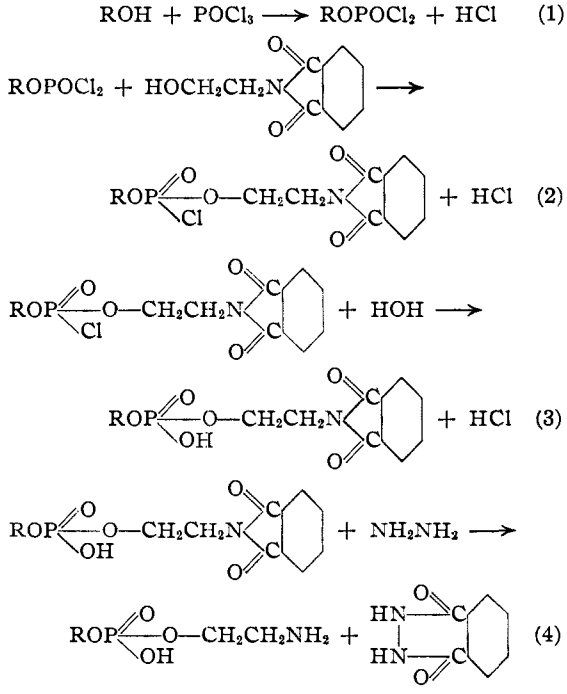
In the present investigation, α,γ-dimyristin was prepared by causing glycerol to react with myristic acid; α,γ-glycerol eruco-stearate was made by a procedure not previously described, which involves treating glycidyl stearate with erucic acid:



$$H_2C\text{—}CH\text{—}CH_2OOCR + HOOCR' \longrightarrow R'COOCH_2CHOHCH_2OOCR$$

This reaction proceeded smoothly in the temperature range of 125–135°. Best results were obtained with a two-fold excess of glycidyl ester, and by refluxing in chlorobenzene solution. When the acid had almost disappeared, the solvent was boiled off under reduced pressure and the diglyceride was isolated by crystallizing twice from hexane and finally from alcohol.

The synthesis of cephalins from both dimyristin and glycerol eruco-stearate was accomplished according to the Rose procedure in a series of consecutive reactions but these were performed without isolation of intermediate compounds



$$ROH + POCl_3 \longrightarrow ROPOCl_2 + HCl \quad (1)$$

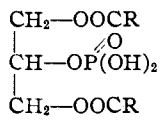
$$ROPOCl_2 + HOCH_2CH_2N(CO)_2C_6H_4 \longrightarrow ROP(O)(Cl)\text{—}O\text{—}CH_2CH_2N(CO)_2C_6H_4 + HCl \quad (2)$$

$$ROP(O)(Cl)\text{—}O\text{—}CH_2CH_2N(CO)_2C_6H_4 + HOH \longrightarrow ROP(O)(OH)\text{—}O\text{—}CH_2CH_2N(CO)_2C_6H_4 + HCl \quad (3)$$

$$ROP(O)(OH)\text{—}O\text{—}CH_2CH_2N(CO)_2C_6H_4 + NH_2NH_2 \longrightarrow ROP(O)(OH)\text{—}O\text{—}CH_2CH_2NH_2 + HN(CO)_2C_6H_4NH \quad (4)$$

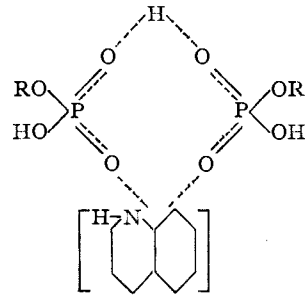
Carrying through the reactions as described (that is, without isolating and purifying the intermediate phthal derivative) resulted in a considerably higher yield of product; the time consumed in performing the synthesis was shortened, and no emulsion problems were encountered.

As part of the experimentation during synthesis of cephalins, isolation of some of the intermediates formed in the reactions was attempted. None of the compounds containing the phosphorus–chloride linkage was obtained pure but the hydrolysis product of $ROPOCl_2$, *viz.*, dimyristin phosphatidic acid was isolated as its half-quinolin-



$$CH_2\text{—}OOCR$$
$$CH\text{—}OP(O)(OH)_2$$
$$CH_2\text{—}OOCR$$

ium salt. This compound contains two molecules of phosphatidic acid combined with one of quinoline, probably having the hydrogen bridge structure postulated by Wagner-Jauregg and Wildemuth[4] for the sodium "superacid salt" of cetyl and cholesteryl phosphate. A previous similar observation had been made by Tipson,[5] who obtained a salt containing two molecules of nucleotide combined with one of aromatic base. According to the theory of Wagner-Jauregg and Wildemuth, the quinolinium phosphatidate of dimyristin would have the structure



It was found exceedingly difficult to prepare phosphatidic acids in pure form. Acidification of an alcoholic solution of the quinolinium salt with hydrochloric acid did not remove the base completely. Nitrogen-free sodium and barium salts were obtained but these did not yield pure acids. Phthal-cephalins (reaction 3) gave evidence of instability, as indicated by a spontaneous drop in neutral equivalent during short periods of storage.

Experimental

Myristic Acid.—Methyl esters of commercial 90% myristic acid were fractionated with the aid of a three-foot Stedman column. Fractions of appropriate saponification value and boiling range were hydrolyzed with alkali, and the recovered acids were crystallized from acetone: m. p. 53.8–54.6°; neut. eq., 229. Calcd. for myristic acid, neut. eq., 228.36.

Stearic Acid.—Commercial 90% stearic acid was fractionally recrystallized from absolute alcohol: m. p. 69.5–69.7°; neut. eq., 284.7. Calcd. for stearic acid, neut. eq., 284.47.

(4) Wagner-Jauregg and Wildemuth, *Ber.*, **77**, 481 (1944).

(5) Tipson, *J. Biol. Chem.*, **120**, 621 (1937).

Erucic Acid.—Rape oil was treated to obtain erucic acid according to the method of Ross, *et al.*[6]: the product melted at 33.5–34.5°.

Anal. Calcd. for erucic acid: neut. eq., 338.56; iodine value, 74.9. Found: neut. eq., 338.5; iodine value, 72.9.

β-Hydroxyethylphthalimide.—The procedure of Rose[3] was used for making this compound. The purified product melted at 126.5–127°.

α,γ-Dimyristin.—In a 500-ml. flask were mixed 171 g. (0.75 mole) of myristic acid and 207 g. (2.25 moles) of redistilled glycerol. The flask was fitted with a mechanical stirrer and a gas inlet tube through which nitrogen was passed. The mixture was heated with stirring on an oil-bath for five hours at 195–200°. At the end of the reaction the flask contained an oily layer and one consisting principally of glycerol. Both were practically neutral. The contents of the flask were stirred into 400 ml. of hexane and washed with three 200-ml. portions of water to remove unreacted glycerol. The solution of glycerides was dried, then allowed to stand for three hours at room temperature, and filtered with suction. The precipitate was washed with two 50-ml. portions of hexane and air-dried. The product, crude dimyristin, 140 g., was purified by two recrystallizations from absolute alcohol, and finally from hexane; yield of product, 39 g. (20% on basis of myristic acid used); m. p., 66.1–66.3°. Periodate analysis showed absence of monoglyceride.

Anal. Calcd. for dimyristin, $C_{31}H_{60}O_6$: C, 72.6; H, 11.8; sapn. equiv. wt., 256.4; combined fatty acids, 89.2%. Found: C, 72.8; H, 11.8; sapn. equiv. wt., 256.5; combined fatty acids, 89.4%.

Glycidyl Stearate.—This compound was prepared according to the method of Kester, *et al.*[7] From 191 g. (0.592 mole) of potassium stearate and 545 g. (5.89 moles) of epichlorohydrin was obtained 102 g. of purified glycidyl stearate (50% yield); m. p. 54.7–55°.

Glycerol α,γ-Erucostearate.—To 1000 ml. of chlorobenzene contained in a 2-liter flask fitted with reflux condenser, were added 85 g. (0.251 mole) of erucic acid and 170 g. (0.502 mole) of glycidyl stearate. The mixture was refluxed gently for twenty-eight hours. At the end of this time, a titrated sample showed the reaction to be 99% complete. Solvent was removed by distillation at about 20 mm. pressure. The residue, 260 g., was crystallized from 780 ml. of hexane at 23–25° over a sixteen-hour period. The product was filtered with suction, washed twice with 100-ml. portions of hexane, and air-dried; m. p. 50–57°.[8] A second crop was obtained by concentrating the liquors to half their volume. The two crops were combined, crystallized once from 240 ml. of hexane at 23–25° over a period of sixteen hours, and again from 200 ml. of absolute alcohol at 23–25°. The purified diglyceride weighed 65 g. (40% of calculated amount); m. p., 56–57°.

Anal. Calcd. for $C_{43}H_{82}O_5$: C, 76.0; H, 12.2; iodine value, 37.3; sapn. equiv. wt., 339.5. Found: C, 76.1; H, 12.1; iodine value, 36.2; sapn. equiv. wt., 341.

Recovery of Unreacted Glycidyl Stearate.—The various filtrates from the above purification were combined and evaporated to dryness on a steam-bath. The residue, 152 g., was distilled at 160–175° and 0.1 mm. pressure. The distillate was crystallized twice from absolute alcohol at 23–25° for sixteen hours; yield, 40 g. (50% of the glycidyl stearate used in excess); m. p., 54–55°; sapn. equiv. wt. 341.

α,γ-Dimyristocephalin.—In a 500-ml. 3-necked flask fitted with a mechanically driven stirring device, dropping funnel (all previously oven-dried), and a drying tube filled with desiccant, were placed 25 ml. of alcohol-free chloroform and 2.98 g. of phosphorus oxychloride. The flask was surrounded by an ice-bath, and the solution was cooled to below 5° with stirring. Ten ml. of pyridine, dried over barium oxide, was added dropwise. At the end of the addition the ice-bath was replaced with a cold-water-bath to raise the temperature to 10–15° where it was maintained throughout the dropwise addition of a solution of 10 g. (0.0195 mole) of dimyristin in 100 ml. of alcohol-free chloroform, over a sixty-minute period. The bath was then warmed to 25° where it was kept for thirty minutes, stirring being continued. The reaction mixture was now raised to a temperature of 40°, by adjusting the bath, and maintained at this point for another thirty-minute period, after which the temperature was lowered to 10–15°, and 7.44 g. (0.039 mole) of β-hydroxyethylphthalimide, dissolved in 200 ml. of alcohol-free chloroform, was introduced dropwise over a period of one hour. The mixture was stirred for an additional half hour with the bath temperature at 30° and then for another half hour at 40°. The solvent was partially removed at room temperature by means of a water pump, and finally with a mechanical vacuum pump until the last traces of chloroform had disappeared.

The residue was added to a slurry of 300 ml. of *N* hydrochloric acid plus finely chopped ice and mixed in a laboratory blender which was kept in operation at slow speed for an hour. The temperature was not allowed to rise above 5°. A fine granular precipitate resulted which was separated from the liquid by vacuum filtration conducted in a refrigerator. It was washed with ice water until the washings were chloride-free and almost neutral to litmus. The wet filter cake, crude phthalcephalin, was dissolved in 200 ml. of neutral glycol monomethyl ether, and 39 ml. of 0.5 *N* sodium hydroxide[9] was added dropwise with stirring over a period of ninety minutes. Twenty-eight ml. of 1.5 *M* hydrazine hydrate solution was then introduced and the mixture gently refluxed in a 500-ml. flask for an hour. It was cooled and allowed to stand overnight, during which time crude dimyristo-cephalin deposited on the walls of the flask. The solid material was separated from the liquid by centrifuging, washed four times with 50-ml. portions of acetone–water (1:1), and then with four 50-ml. portions of acetone. The cephalin was purified by crystallization out of alcohol at room temperature. It formed characteristic spherulites exhibiting birefringence under polarized light (Fig. 1); yield, 5.2 g., or 40% calculated on the basis of the dimyristin taken; m. p., 173–174°.[10]

Anal. Calcd. for $C_{33}H_{66}O_8NP$: C, 62.3; H, 10.5; P, 4.87; N, 2.20. Found: C, 61.6; H, 10.2; P, 4.84; N, 2.11.

α,γ-Eruco-stearo-cephalin.—Forty grams (0.0589 mole) of glycerol erucostearate was subjected to the series of reactions described under "dimyristocephalin," under the conditions specified including the hydrazine treatment in glycol-monomethyl ether. After this reaction, an oily material separated from the hot solution, and was removed without prior cooling. On standing overnight at room temperature, it partially solidified to a paste-like mass. This material was alternately mixed and centrifuged with three 50-ml. portions of acetone–water solution (1:1) and finally with two of pure acetone. The product was allowed to air-dry and crystallized three times from 500 ml. of absolute alcohol. The yield was 12.6 g. or 25%, calculated on the basis of the glycerol eruco-stearate taken, m. p. 163.5–164°. The cephalin crystallized in spherulites, sometimes singly, but more often as botryoidal clusters, similar to those of dimyristo-cephalin.

Anal. Calcd. for $C_{45}H_{88}O_8NP$: C, 67.4; H, 11.0; P,

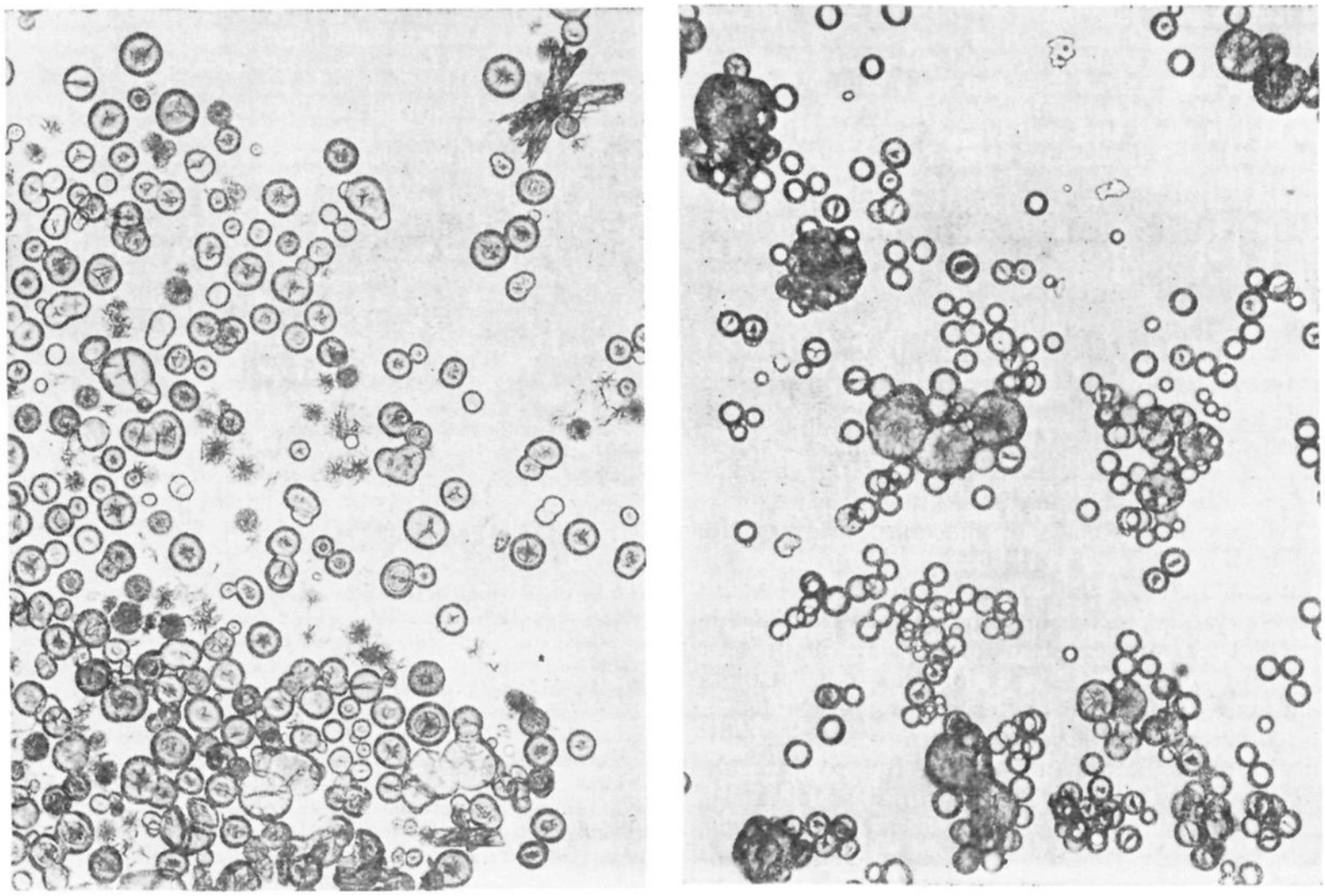
(6) Ross, Gebhart and Gerecht, THIS JOURNAL, **67**, 1275 (1945).

(7) Kester, Gaiser and Lazar, *J. Org. Chem.*, **8**, 550 (1943).

(8) If the melting point of this product exceeds 57°, the presence of monostearin is indicated. In this case, the material should be dissolved in ten times its weight of benzene, the solution seeded with monostearin, and, after filtering off the precipitate that develops, evaporated to dryness.

(9) Calculated by assuming 100% conversion of dimyristin to phthalcephalin.

(10) The cephalins tend to darken somewhat below their melting point if open capillary tubes are used for the determination. It was found that this could be avoided if the tubes were evacuated, flushed with nitrogen repeatedly, and sealed off after a final evacuation.



Incompletely purified Pure.

Fig. 1.—Photomicrograph of dimyristocephalin.

3.86; N, 1.75; iodine value, 31.3. Found: C, 67.0; H, 11.0; P, 3.8; N, 1.72; iodine value,[11] 29.1.

Dimyristo-phosphatidic Acid, Half Quinolinium Salt.—In an oven-dried, 500-ml., three-necked flask, fitted with mechanical stirrer, separatory funnel, and calcium chloride tube, were placed 25 ml. of alcohol-free chloroform and 22.7 ml. (0.0913 mole) of phosphorus oxychloride. The flask was immersed in an ice-bath, and 30.5 g. of quinoline (C. P. grade) was added dropwise with vigorous stirring. The bath temperature was then raised to 10° and maintained at 10–15° during the addition of 14.0 g. (0.0273 mole) of dimyristin in 100 ml. of chloroform, over a one-hour period. The temperature of the bath was now raised to 30° and maintained at this point for an additional hour. Solvent was removed by distillation under reduced pressure and finally at 1–5 mm. with the aid of a mechanical pump. During this operation the contents of the flask were not warmed to temperatures higher than that of the room. The residue was transferred to a blender and mixed intimately with 200 ml. of *N* hydrochloric acid at 0–5°. The granular precipitate which resulted was filtered with suction, washed with water, air-dried and recrystallized three times from five times its weight of ethyl acetate; yield, 17.3 g. or 62%; m. p. 96.6–97.5°.

Anal. Calcd. for $C_{71}H_{129}O_{16}P_2N$: C, 64.9; H, 9.9; P, 4.71; N, 1.06; neut. eq., 328.7. Found: C, 64.5; H, 9.8; P, 4.81; N, 1.00; neut. eq., 327.6.

(11) It was observed that eruco-stearo-cephalin when repeatedly recrystallized from alcohol showed a progressive reduction in iodine value amounting to about one unit for each treatment.

Acknowledgment.—The assistance of Elizabeth A. McComb, Geraldine Secor and L. M. White in the analyses, and that of F. T. Jones in the microscopic and optical examination of the products described in this investigation are gratefully acknowledged.

Summary

The preparation of dimyristo-cephalin and eruco-stearo-cephalin has been described.

A new method for preparing diglycerides of dissimilar fatty acids has been applied to the synthesis of glycerol α,γ-erucostearate.

It has been shown that dimyristin-phosphatidic acid forms a stable half-quinolinium salt.

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