sulfide mineral from the Horobetsu sulfur mine (Hokkaidô, Japan) with success.

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Synthesis of Enantiomeric α-Cephalins[1]

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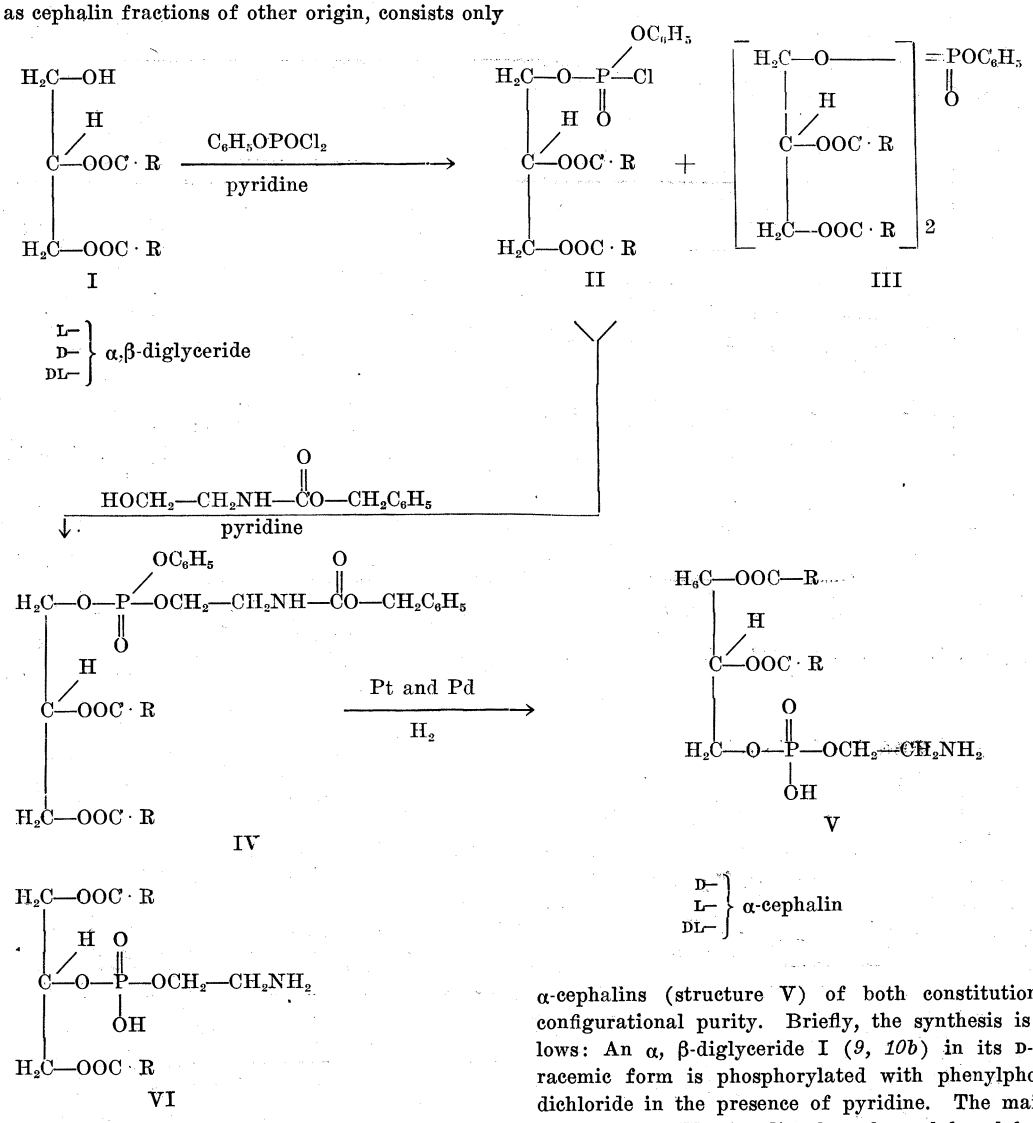
Folch (*1–4*), Wooley (*2, 5*), Hutt (*6*), and their associates have shown that Thudichum's ox brain cephalin, as well as cephalin fractions of other origin, consists only partially of phosphatidyl ethanolamine, which is known classically as cephalin and to which have been assigned structures V and VI. Associated with it are variable amounts of phosphatidyl serine and other complex phosphoric acid esters containing inositol, galactose, and as yet unidentified nitrogenous constituents. A study of the biological role of the various components of the "cephalin fraction" requires accessibility to the pure substances. The difficulties encountered in isolating pure individual cephalins (phosphatidyl ethanolamines) from natural sources have prompted several attempts (*7, 8*) to obtain these compounds by synthesis. None of these attempts to synthesize the α-cephalins, however, can be considered truly successful.

The authors herein report a procedure which is generally applicable to the synthesis of fully saturated



α-cephalins (structure V) of both constitutional and configurational purity. Briefly, the synthesis is as follows: An α, β-diglyceride I (*9, 10b*) in its D-, L-, or racemic form is phosphorylated with phenylphosphoryl dichloride in the presence of pyridine. The main reaction product II, the diacyl α-glycerylphenylphosphoryl chloride, without isolation from III, is immediately

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esterified with carbobenzoxyethanolamine (*11*). The reaction mixture is brought to dryness *in vacuo*, the diacyl α-glycerylphenylphosphoryl carbobenzoxyethanolamine IV is isolated by extraction with petroleum ether and is freed from impurities by treatment with ethyl acetate. The simultaneous removal of the protective phenyl- and carbobenzoxy groups by catalytic hydrogenolysis in the presence of platinum and palladium yields the desired α-cephalins V in over-all yields of 48–51%. The cephalins after precipitation from chloroform with acetone and recrystallization from dioxane are obtained in the form of microscopic spherulites, which exhibit birefringence under polarized light.

The following three L-α-cephalins were synthesized:

1. L-α-distearoyl cephalin (DSC) ÷ C_{41} H_{82} O_8 NP. Found: C, 65.79; H, 10.80; N, 1.89; P, 4.16. $[\alpha]_D^{24}$ + 6.0° in chloroform-acetic acid (7:1) c, 4.4; M_D + 44.5°. Starts to sinter at 83°, melts with meniscus formation at 172°–175°.

2. L-α-dipalmitoyl cephalin (DPC) ÷ C_{37} H_{74} O_8 NP. Found: C, 64.15; H, 10.66; N, 1.85; P, 4.50. $[\alpha]_D^{26}$ + 6.4° in chloroform c, 7.8; M_D + 43.5°. Sinters at 88°, meniscus formation at 172°–175°.

3. L-α-dimyristoyl cephalin (DMC) ÷ C_{33} H_{66} O_8 NP. Found: C, 62.16; H, 10.41; N, 2.10; P, 4.85. $[\alpha]_D^{26}$ + 6.7° in chloroform c, 8.4; M_D + 42.5°. Sinters at 86°, meniscus formation at 175°–177°.

The three synthetic cephalins after recrystallization from warm dioxane gave distinct x-ray diffraction patterns; Debye-Scherrer powder camera (114.5-mm), radiation CuK_α (λ 1.54K_x) nickel filter. Actual diameters in centimeters as measured on the original photographs and visually estimated relative intensities (in parentheses): Distearoyl L-α-cephalin 3.93 (0.3), 4.31 (1.0), 4.66 (0.5), 5.62 (0.1), 8.06 (0.1), 9.17 (0.3), 10.65 (0.1); dipalmitoyl L-α-cephalin 3.83 (0.4), 4.30 (1.0), 4.76 (0.4), 5.66 (0.4), 6.39 (0.1), 7.23 (0.1), 8.10 (0.3), 10.02 (0.1); dimyristoyl L-α-cephalin 3.03 (0.3), 3.46 (0.3), 3.74 (0.5), 4.34 (1.0), 4.65 (0.7), 5.98 (0.2), 7.41 (0.1), 8.00 (0.1), 9.21 (0.3).

The approximate solubilities of the synthetic L-α-cephalins in various solvents at 20° were determined. The cephalins were found to be insoluble ($\leqq$ 1 mg/100 ml of dry solvent) in acetone, ether, petroleum ether, and ethyl acetate; moderately soluble (20 mg–1,000 mg/100 ml of dry solvent) in ethanol, pyridine, benzene, and carbon tetrachloride, and readily soluble ($>$ 1 g/100 ml of solvent) in chloroform. The solubility of the cephalins increases with decreasing length of the fatty acid chain. As might have been anticipated, the three synthetic α-cephalins are considerably less soluble than the corresponding α-lecithins (*10 a, b*). It is of interest to note in this connection that Folch has reported that the phosphatidyl ethanolamine isolated by him is readily soluble in alcohol. It is possible that this greater solubility of the natural substance is explained by the degree of unsaturation of its fatty acids.

It is well known that glycerol derivatives are optically active only when asymmetrically substituted. As has been discussed more fully elsewhere (*10 a, b*; *12*), asymmetrically trisubstituted derivatives of glycerol can be assigned to either one of the two optical series (D- or L-). Hence in the case of α-cephalins (α-phosphatidyl ethanolamines) any particular member can be considered either as derivative of its diglyceride moiety or of glycerylphosphorylethanolamine (GPEA). The choice made, as in the case of the corresponding α-lecithins (*10 a, b*), has been influenced by biological as well as chemical considerations. Because the GPEA moiety is the same in every α-cephalin, it has been chosen as the stereochemical compound of reference. Thus arbitrarily, but in conformity with the adopted usage in the α-lecithin series (*10 a, b*), an α-cephalin is assigned the L-configuration if it contains L-α-GPEA and the D-configuration if it contains D-α-GPEA.

The synthetic procedure described above makes available for the first time pure enantiomeric forms of individual α-cephalins. The experimental details will be reported shortly elsewhere.

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