$CH(CH_2CH(CH_3)_2)$ and $N^+CH_2(CH_2)_3CH_2CO$], 2.30 [2 H, t, $N^+(CH_2)_4CH_2CO$], 3.39 [9 H, s, $(CH_3)_3N^+$], 2.95–ca. 4.0 [6 H, m, $N^+CH_2(CH_2)_4CO$ and $NCH_2(CH_2)_{10}CH_3$], 4.20–5.15 [3 H, m, $CH(CH_2CH(CH_3)_2)$], 6.78–7.18 (3 H, m, NH).

Registry No. 1, 80997-12-2; 2, 80997-13-3; 3, 80975-61-7; 4, 80975-62-8; 5, 80975-63-9; 6, 80975-64-0; 7, 80975-65-1; $N^+C_5Leu2C_{12}$, 80975-66-2; $CAC_2N^+C_5Leu2C_{12}$, 80975-67-3; $N^+C_5Ala2C_{12}$, 78761-16-7; $CAC_2N^+C_5Ala2C_{12}$, 80975-68-4; $N^+C_5Sar2C_{12}$, 80975-69-5; $CAC_2N^+C_5Sar2C_{12}$, 80975-70-8; $N^+C_5Leu_32C_{12}$, 80975-71-9; *N*-(*tert*-butoxycarbonyl)-L-leucine, 13139-15-6; *N,N*-didodecylamine, 3007-31-6; 6-bromohexanoyl chloride, 22809-37-6; *N*-(*tert*-butoxycarbonyl)-L-alanine, 15761-38-3; *N*-(*tert*-butoxycarbonyl)sarcosine, 13734-36-6; *N,N*-didodecyl-N^α-(*tert*-butoxycarbonyl)-L-alanine, 80975-72-0; *N,N*-didodecyl-N^α-(6-bromohexanoyl)-L-alanine, 80975-73-1; *N,N*-didodecyl-N^α-[6-(dimethylamino)hexanoyl]-L-alaninamide, 80975-74-2; *N,N*-didodecyl-N^α-(*tert*-butoxycarbonyl)sarcosine, 80975-75-3; *N,N*-didodecyl-N^α-(6-bromohexanoyl)sarcosine, 80975-76-4; *N,N*-didodecyl-N^α-[6-(dimethylamino)hexanoyl]sarcosinamide, 80975-77-5.

Syntheses of Enzyme-Inhibitory Phospholipid Analogues. Stereospecific Synthesis of 2-Amidophosphatidylcholines and Related Derivatives

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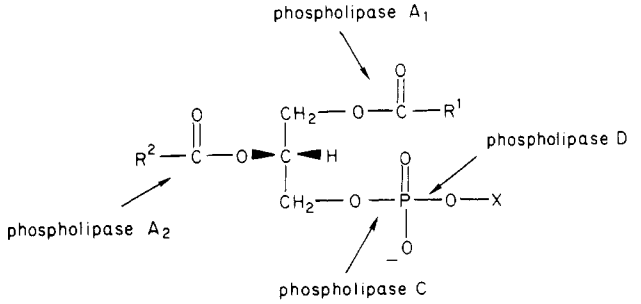
A novel stereospecific synthesis of the enzyme-inhibitory 2-*sn*-deoxy-2-amidophosphatidylcholine is reported. The synthesis is based on (1) utilizing the chirality of the α-carbon of the starting amino acid serine, (2) protecting the asymmetric center via formation of an oxazoline ring, and (3) introducing the phosphorylcholine moiety through the 2-chloro-2-oxo-1,3,2-dioxaphospholane–trimethylamine sequence. The compound has been shown to be a specific and potent phospholipase A_2 inhibitor, exhibiting higher affinity to the enzyme under the reaction conditions than the natural substrate. The synthetic method used for the preparation of the inhibitor provides a general route to a wide range of other phospholipid analogues as well. Along these lines 2-deoxy-2-aminolysolecithin has been shown to react with octyl chloroformate and stearoyl isocyanate to form the corresponding 2-*sn*-carbamoyl and 2-*sn*-alkylureido derivatives. The scope of the synthesis is being investigated for the preparation of reversible as well as irreversible phospholipase inhibitors.

The synthesis of enzyme-inhibitory phospholipid analogues is one of the most timely problems in membrane biochemistry today.[1,2] Nonhydrolyzable isosteric phospholipid derivatives are required for structural as well as dynamic studies of biomembranes and membrane-bound enzymes, with particular emphasis on investigation of phospholipid–phospholipid and phospholipid–protein interactions.[3] As part of our ongoing research aimed at the elucidation of the mechanism of action of phospholipase A_2,[4,5] we have recently began focusing our efforts on the development of new synthetic methods for the preparation of specific and potent inhibitory phospholipid analogues.[6]

Specifically, phospholipase A_2 is one of the four phospholipid hydrolyzing enzymes. Its unique biological importance arises from the fact that it also participates in a number of physiologically vital regulatory processes,[7-11] including platelet aggregation, cardiac contraction and excitation, prostaglandin biosynthesis, and aldosterone-dependent sodium transport. Availability of specific and potent phospholipase A_2 inhibitors, therefore, should be valuable for delineation of the precise function of the enzyme in vivo and for kinetic studies aimed at the elucidation of its catalytic mechanism in vitro.



1

X = choline, serine, ethanolamine

Utilizing a new approach to the problem, we have recently accomplished the stereospecific synthesis of the first series of inhibitory 2-deoxyamidophosphatidylcholines.[6] In the present article we describe the synthesis of compound **2** in detail and demonstrate the applicability of the method for the preparation of a series of other related phospholipid analogues as well.

Results and Discussion

The structural design of **2** as our target compound has originated from early studies by de Haas and van Deenen, who have demonstrated, using short-chain lecithin analogues, that replacement of the ester moiety by the corresponding amide function at the catalytic 2-position abolishes the catalytic hydrolysis by the enzyme.[13]

Our synthetic approach to the preparation of **2** is based on the recognition that the chirality of the optically active α-carbon in L-serine (**3**) is identical with that of the asymmetric center in the desired phospholipid analogue **2**. Consequently, our strategy for the preparation of **2** is based on construction of the chiral amidophospholipid

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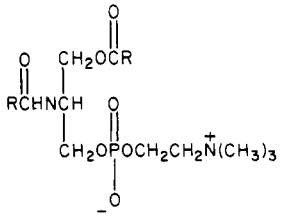
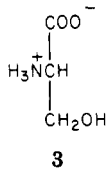


2



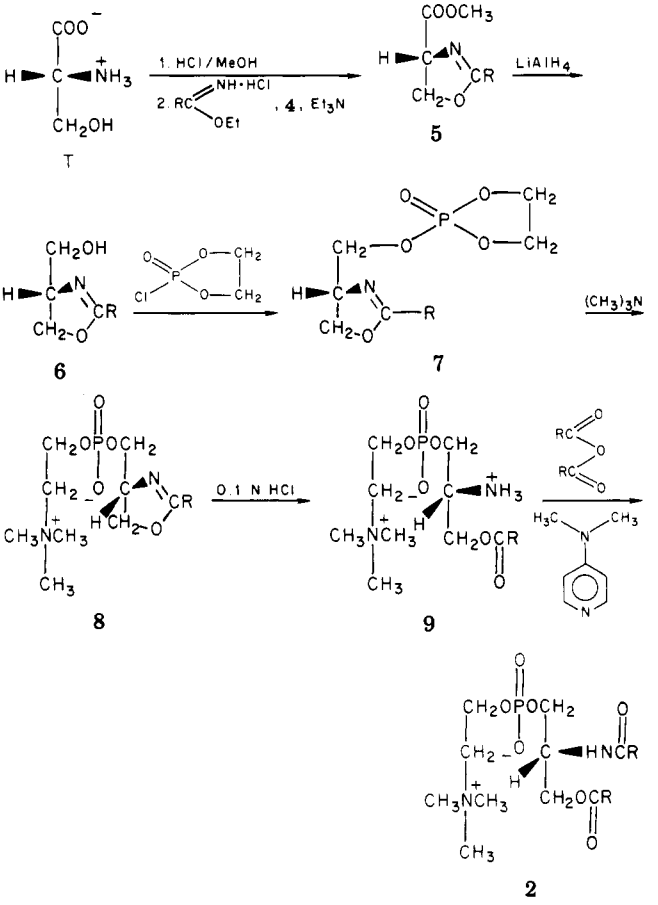
3

skeleton around the serine nucleus (Scheme I). Considering the structural relationship between **3** and **2**, the procedure must involve (1) reduction of the carboxylic function without destroying the chirality of the asymmetric α-carbon, (2) introduction of the phosphodiester moiety, and (3) acylation of the 2-amino and 1-hydroxylmethyl function to obtain the desired phospholipid derivative.

In order to achieve these goals it appeared that introduction of an oxazoline function at the amino alcohol moiety of the starting amino acid could best fulfill the requirements outlined. Thus, formation of **5** in the sequence accomplishes a number of objectives: (1) it serves as a protecting group for both amino and hydroxy functions, (2) it prevents the loss of asymmetry at the chiral center, on reduction, and (3) it serves as the precursor for the incipient carboxylic ester substituent of the final product. Preparation of **5** was readily accomplished by condensation of the imino ether **4**[14] with serine methyl ester in good yield (75%). The alternative procedure involving acid-catalyzed cyclization of the corresponding fatty acid amide was found a great deal less efficient.

Lithium aluminum hydride reduction of **5**[15] led to the formation of the hydroxymethyl-substitued oxazoline **6** in essentially quantitative yield. This step was followed by the introduction of the phosphorylcholine function via the 2-chloro-2-oxo-1,3,2-dioxaphospholane–trimethylamine sequence. We have found this cyclic phosphochloridate to be by far the most suitable reagent for the phosphorylation of **6**. It is a great deal more reactive under the reaction conditions than the more commonly used (β-bromoethyl)phosphodichloridate.[13] Thus, formation of the cyclic phosphotriester is complete within 2 h at room temperature in benzene with 1 equiv of triethylamine used as catalyst. Compound **7**, obtained as a single phosphate-positive[18] product is isolated from the reaction mixture in quantitative yield. Ring opening of the ethylene-bridged phosphate diester portion of the molecule by anhydrous trimethylamine, in acetonitrile at 65 °C for 24 h, has readily yielded **8**. This product could be used directly[19] for the hydrolysis of the oxazoline moiety which was accomplished in aqueous soluiton with 1 equiv of 0.1 N HCl. The deoxy amino analogue of lysolecithin **9** was isolated as a single ninhydrin- and phosphate-positive product. The amino group of this compound, probably due to steric hindrance, is remarkably unreactive under normal acylation conditions.[20] It can be readily converted to the corresponding amide, however, in the presence of 4-(dimethylamino)pyridine with either anhydride[20] or carboxylic acid halide[21] at ambient temperatures in high yield. We have found that chromatographic purification was only necessary in the final step of the sequence.

Scheme I. Synthesis of 2-Deoxy-2-amidophosphatidylcholine (2) from Serine[a]



[a] R = $CH_3(CH_2)_{16}$.

The most important synthetic strategy that has emerged from this sequence is the use of the oxazoline function for both protecting the chiral amino alcohol moiety and providing the incipient carboxylic ester function at the 1-*sn*-position of the phospholipid derivative. While the synthetic scheme represents an efficient procedure for the preparation of 2-*sn*-amidophosphatidylcholines, some of the intermediates provide useful precursors for the synthesis of other phospholipids as well. Specifically, further functionalization of the hydroxymethyl group of **6** (i.e., alkylation, oxidation to the carbonyl function) or the oxazoline nitrogen in either **6** or **8** should produce a series of new 1-*sn*- and 2-*sn*-substituted phospholipid derivatives.[22] Another important intermediate in the sequence is 2-deoxyaminolysolecithin (**9**), which can readily serve as a precursor for a number of 2-substituted reversible as well as covalently reactive irreversible phospholipase inhibitors (see below).

(14) Meyers, A. I.; Whitten, C. E. *Heterocycles* **1976**, *4*, 1687. (b) Elliott, D. F. *J. Chem. Soc.* **1949**, 589.

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(19) We have tried to avoid extensive use of silica gel column chromatography of polar intermediates because of inconsistent recoveries of the phospholipid derivatives.

(20) Similar findings were reported with respect to the reactivity of the 2-*sn*-hydroxylic group in lysophosphatidylcholine (ref 1, Gupta, C. M.; Bali, A. *Biochim. Biophys. Acta* **1981**, *663*, 506–515.

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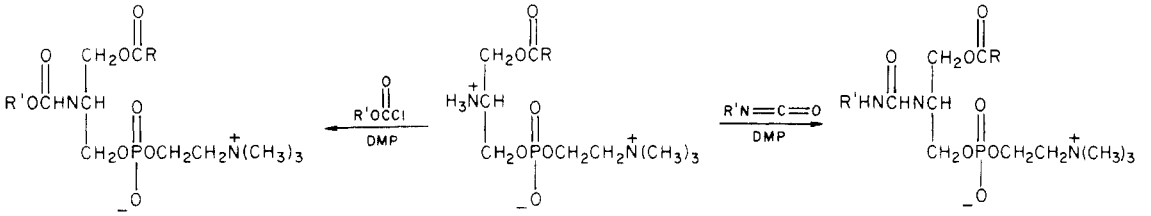
(22) Utilizing the hydroxymethyl-substituted oxazoline intermediate, we have been able to prepare 1-0-alkyl-2-deoxy-2-(aminoacyl)-3-*sn*-phosphatidylcholines. Furthermore, it is important to point out that depending on the configuration of the starting amino acid utilized, the incipient 1- vs. 3-positions of the phospholipid (see 1) are interchangeable. Thus, proper functionalization of the hydroxylmethyl group in **6** derived from either L-serine or D-serine (both commerically available) should readily permit introduction of nonscissile substrate functions blocking phospholipase A_1 and phospholipase C, respectively.

Scheme II. Synthesis of the 2-[[(Octyloxy)carbonyl]amino]- and 2-[[(Octadecylamino)carbonyl]amino]deoxyphosphatidylcholines (10 and 11)



10, R' = $CH_3(CH_2)_7$ 9 11, R' = $CH_3(CH_2)_{17}$

Biological Activity of 2. We have been able to obtain evidence[23] that compound **2** is a potent phospholipase A_2 inhibitor, exhibiting high specificity to the enzyme. 1-Stearoyl-2-stearoyldeoxyaminophosphatidylcholine is not hydrolyzed by cobra venom phospholipase A_2 (*Naja naja naja*). In the experiment using high concentrations of pure enzyme (0.5 mg/2 mL) no reaction was detected over the background after 12 h at 40 °C. However, lipase from *Rhizopus arrhizus* with phospholipase A_1 activity does hydrolyze the compound.

For determination of the inhibitory potency of **2**, a series of assay mixtures containing phospholipase A_2 (*Naja naja naja*) at constant (5 mM) concentration of phosphatidylcholine were titrated with the amidolecithin. A 0.5 mM concentration of **2** was required to decrease the hydrolytic activity of the enzyme by 50%. This indicates that under the experimental conditions the isosteric 2-amide analogue of the substrate is a potent phospholipase A_2 inhibitor.[23]

Preparation of Related Phospholipid Analogue. On the basis of the inhibitory efficiency exhibited by **2** indicating that the nonhydrolyzable amide analgoue appears to have enhanced affinity to the enzyme in comparison with the ester substrate, we have proceeded to prepare the corresponding 2-*sn*-carbamoyl and 2-*sn*-alkylureido derivatives possessing increasingly electron-rich carbonyl groups that are likely to become potent phospholipase A_2 inhibitors.

We have prepared these compounds (Scheme II) from 2-deoxyaminolysolecithin (**9**). As in the case with stearic anhydride, we have found that **9** reacts with alkyl chloroformates and alkyl isocyanates in the presence of 4-(dimethylamino)pyridine to give **10** and **11**, respectively. Both compounds were obtained in good yields and isolated in a manner similar to the one described for the amide analogue **2**. Although their biological activities have not yet been determined, the synthesis of these compounds demonstrates the applicability of **9** for the preparation of an extended scope of functionalized phospholipid analogues.

In conclusion, it might be noted that the strength of the synthetic method that has been described is in its (1) simplicity and efficiency, (2) flexibility in terms of the substituents that can be introduced, and (3) applicability to the development of specific and selective enzyme-inhibitory phospholipid analogues. Synthetic work along these lines is currently underway in our laboratory.

(23) The inhibition studies were carried out in collaboration with Professor E. A. Dennis, University of California, San Diego. For determination of the inhibitory potency of **2** each assay mixture contained 5 mM phosphatidylcholine, 40 mM Triton X-100, and 10 mM $CaCl_2$. For the assay system see Deems, R. A.; Dennis, E. A. *Methods Enzymol.* **1981**, *71*, 703–710.

(24) The analytical result obtained for C is within the range of deviations commonly encountered for phospholipid derivatives. (See, for example, microanalytical data in Bonsen, P. P. M.; Burback-Westerhuis, G. J.; deHaas, G. H.; van Deenen, L. L. M. *Chem. Phys. Lipids* **1972**, *8*, 199–220).

Experimental Section

General Methods. Melting points were determined on a Mel-Temp (Fisher) apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 599B spectrophotometer. ^1H NMR (internal Me_4Si) spectra were taken on a Hitachi Perkin-Elmer R-24 60-MHz instrument. D-Serine was obtained from Sigma Chemical Co. 2-Cyanoheptadecane was obtained from Pfaltz and Bauer, Inc. 4-(Dimethylamino)pyridine (Aldrich), stearoyl isocyanate (Fluka), octyl chloroformate (K & K Laboratories, Long Island, NY), and anhydrous trimethylamine (Eastman) were used as received. Triethylamine (Eastman) and acetonitrile (Burdick & Jackson) were dried over Linde 4A molecular sieves (Ventron). Benzene was distilled from calcium hydride. Chloroform and methylene chloride were distilled from phosphorus pentoxide prior to use. 2-Chloro-2-oxo-1,3,2-dioxaphospholane[16] and stearic anhydride[12] were prepared by literature procedures. Column chromatography was carried out with silica gel 60 (70–230 mesh, ASTM), Sephadex LH-20 (25–100-μm beads), and Rexyn I-300 mixed-bed resin obtained from E.M. Laboratories, Pharmacia, and Fisher, respectively. Thin-layer chromatography was carried out on Whatman K6F plates. The phospholipids were visualized by the molybdic acid spray.[18] Amine-containing compounds were spotted by ninhydrin and all other compounds were detected by charring (50% sulfuric acid) or by iodine vapor. Elemental analyses were performed by Galbraith Laboratores, Inc. and Guelph Chemical Laboratories, Ltd.

Ethyl Octadecanimidate Hydrochloride (4). Through a mixture of 1-cyanoheptadecane (10.05 g, 37 mmol) and absolute ethanol (1.75 g, 38 mmol) in 50 mL of absolute ether, cooled to 0 °C, was passed a thin stream of dry HCl gas for 5 h. The ether was then removed in vacuo and the residue was recrystallized from acetone to give 10.65 g of **4** (81%) as a colorless solid (mp 91 °C): IR (Nujol) 1655 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.85 (m, 36 H), 2.7 (br t, 2 H), 4.65 (q, 2 H).

Anal. Calcd for $C_{20}H_{42}ClNO$: C, 69.02; H, 12.17; N, 4.02. Found: C, 68.93; H, 12.21; N, 4.01.

2-Heptadecyl-4-(carbomethoxy)-2-oxazoline (5). To a stirred suspension of the imino ether (9.7 g, 27.95 mmol) and methyl D-serinate hydrochloride (4.333 g, 27.95 mmol) in 250 mL of dry methylene chloride was added dropwise triethylamine (5.647 g, 55.91 mmol) in 10 mL of methylene chloride. The mixture was stirred overnight at room temperature. The solvent was then removed in vacuo, and the residue was extracted with ether (4 × 150 mL). Th extract was dried and the solvent removed in vacuo to give a colorless solid, which was recrystallized from acetone to provide 7.7 g (75%) of the pure ester **5**: mp 42 °C; IR (Nujol) 1742, 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.75 (m, 33 H), 2.25 (br t, 2 H), 3.70 (s, 3 H), 4.4 (m, 3 H).

Anal. Calcd for $C_{22}H_{41}NO_3$: C, 71.89; H, 11.15; N, 3.81. Found: C, 71.73; H, 11.07; N, 3.72.

2-Heptadecyl-4-(hydroxymethyl)-2-oxazoline (6). Lithium aluminum hydride (0.18 g, 4.75 mmol) was added in one portion to a stirred solution of ester **5** (3.3 g, 9 mmol) in 150 mL of ether, cooled to 0 °C, under nitrogen. The mixture was stirred for 2 h at 15 °C and then quenched by adding 25 mL of moist ether, followed by 25 mL of water. The ether layer was separated, and the aqueous layer was stirred with ether (3 × 50 mL). The combined ether extract was washed with 100 mL of saturated NaCl solution and dried. Removal of the solvent in vacuo gave the crude alcohol as a colorless solid. Recrystallization from acetone gave 3 g (98%) of **6** as a colorless crystalline solid: mp

69.5 °C; IR (Nujol) 3220, 1670 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.8 (m, 34 H), 2.2 (br t, 2 H), 3.6–4.5 (m, 5 H).

Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.28; 12.17; N, 4.12. Found: C, 74.08; H, 12.16; N, 4.06.

Phosphate Triester 7. To a stirred mixture of alcohol **6** (1.1325 g, 3.34 mmol) and triethylamine (0.3374 g, 3.34 mmol) in 50 mL of dry benzene, cooled to 0 °C, was added 2-chloro-2-oxo-1,3,2-dioxaphospholane (0.4744 g, 3.34 mmol) in 2 mL of benzene in one portion. The mixture was stirred at room temperature for 2 h. The precipitated triethylamine hydrochloride was filtered off and the filtrate evaporated in vacuo to give the phosphate triester **7** (1.48 g, 100%) as a white solid: NMR ($CDCl_3$) δ 0.7–1.7 (m, 33 H, 2.25 (br t, 2 H), 4.25 (m, 9 H). The compound was used for the next step directly.

Phosphorylcholine 8. Phosphate triester **7** (1.45 g) was transferred with 50 mL of dry acetonitrile into a pressure bottle and 1 mL of anhydrous trimethylamine was added to it. The pressure bottle was left in an oil bath at 65 °C overnight. Cooling and filtration of the precipitated product gave 1.31 g of the crude oxazolinephosphorylcholine **8** as a white solid: IR (Nujol 1665 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.7 (m, 33 H), 2.25 (br t, 2 H), 3.35 (s, 9 H), 3.4–4.2 (m, 9 H); R_f($CHCl_3$–MeOH–H_2O, 65:25:4) 0.28, R_f($CHCl_3$–MeOH–aqueous NH_3, 1:9:1) 0.33. The material was used without purification.

1-Stearoyl-2-deoxy-2-aminophosphatidylcholine Hydrochloride (9). A 334-mg sample of phosphorylcholine **8** was stirred with 7 mL of 0.1 N HCl (1 equiv) for 48 h. The water was then removed by coevaporation several times with ethanol to give 370 mg of crude amino phosphorylcholine **9** as a colorless solid: IR (Nujol) 3360 (br), 1740 cm^{-1}; NMR ($CDCl_3$ + CD_3OD) δ 0.8–1.6 (m, 33 H), 2.25 (br t, 2 H), 3.15 (s, 9 H), 3.2–4.2 (m, 13 H); R_f($CHCl_3$–MeOH–aqueous NH_3, 1:9:1) 0.27. This material was used without further treatment.

1-Stearoyl-2-(stearoylamino)-2-deoxyphosphatidylcholine (2). A mixture of aminophosphorylcholine hydrochloride **9** (334 mg, 0.6 mmol), stearic anhydride (49 mg, 0.9 mmol), and 4-(dimethylamino)pyridine (150 mg, 1.22 mmol) in 25 mL of chloroform was stirred in the dark for 48 h. The solvent was then removed in vacuo. The residue was dissolved in 25 mL of methanol–chloroform–water (5:4:1, v/v) and passed through a column of Rexyn 1-300 resin (75 mL). The resin was washed with two bed volumes of the same solvent. After removal of the solvent in vacuo, the residue was chromatographed on a Sephadex LH-20 column (65 × 1.3 cm) to give 260 mg (55%) of 2-*sn*-amidophosphatidylcholine **2** as a colorless solid: IR (Nujol) 3270 (br), 1735, 1650 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ 0.7–1.65 (m, 66 H), 1.9–2.3 (m, 4 H), 3.10 (s, 9 H), 3.2–4.3 (m, 10 H); R_f($CHCl_3$–MeOH–water, 65:25:4) 0.69, R_f($CHCl_3$–MeOH–aqueous NH_3, 1:9:1) 0.30; $[\alpha]^{25}_D$ −9.11° (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{44}H_{89}N_2O_7P \cdot H_2O$: C, 65.47; H, 11.36; N, 3.47; P, 3.84. Found: C, 65.01; H, 11.28; N, 3.45; P, 3.81.[24]

2-[[(Octyloxy)carbonyl]amino]deoxylecithin (10). A mixture of aminophosphorylcholine hydrochloride **9** (120 mg, 0.215 mmol), octyl chloroformate (60 mg, 0.31 mmol), and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) in 25 mL of chloroform was stirred in the dark for 48 h. The solvent was removed and the residue dissolved in 100 mL of $CHCl_3$–MeOH–water (4:5:1, v/v) and passed through a column of Rexyn 1-300 resin (75 mL). The resin was washed 3 times with a 100-mL portion of the same solvent. After removal of the solvent, the residual product was chromatographed over silica gel (5 g) to give the carbamoyl derivative as a waxy solid: 85 mg (58%); IR (Nujol) 3460 (br), 1710 (br) cm^{-1}; NMR ($CDCl_3$–CD_3OD) 0.7–1.7 (m, 48 H), 2.1 (br t, 2 H), 3.0 (s, 9 H), 3.1–4.3 (m, 12 H); R_f($CHCl_3$–MeOH–water, 65:25:4) 0.69, R_f($CHCl_3$–MeOH–aqueous NH_3, 1:9:1) 0.38.

Anal. Calcd for $C_{35}H_{71}N_2OP \cdot H_2O$: C, 60.32; H, 10.77; N, 4.02; P, 4.44. Found: C, 60.32; H, 10.75; N, 4.20; P, 4.40.

2-[[(Octadecylamino)carbonyl]amino]deoxylecithin (11). A mixture of aminophosphorylcholine hydrochloride **9** and 4-(dimethylamino)pyridine (55 mg, 0.45 mmol) in 30 mL of chloroform was stirred in the dark for 48 h. The solvent was removed in vacuo, and the residue was dissolved in 100 mL of $CHCl_3$–MeOH–water (4:5:1, v/v) and passed through a column of Rexyn 1-300 resin (75 mL). The resin was washed 3 times with a 75-mL portion of the same solvent mixture. After removal of the solvent, the residue was triturated with pentane (50 mL) followed by acetone (50 mL). The residual solid was then chromatographed over silica gel (5 g) to give urea derivative **11** as a colorless solid: 108 mg (60%); IR (Nujol) 3330, 1735, 1635 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ 0.6–1.5 (m, 68 H), 2.1 (br t, 2 H), 2.95 (s, 9 H), 3.0–4.2 (m, 13 H); R_f($CHCl_3$–MeOH–water, 65:25:4) 0.69.

Anal. Calcd for $C_{45}H_{92}N_3O_7P \cdot H_2O$: C, 64.63; H, 11.09; N, 5.03; P, 3.70. Found: C, 65.02; H, 11.04; N, 5.12; P, 3.71.[24]

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N-Hydroxytryptophan in the Synthesis of Natural Products Containing Oxidized Dioxopiperazines. An Approach to the Neoechinulin and Sporidesmin Series

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N-Hydroxytryptophan derivatives have been synthesized via two routes. In one procedure, the indole-3-pyruvate oximes **14b,c** were reduced with trimethylamine–borane in the presence of ethanolic HCl to give **18** (Scheme III); aminolysis of the latter afforded **19**. The second route features the reaction of *N*-methylindole (**20**) with the α-amino-β-bromopropionate **21** to yield **22** (Scheme IV). Subsequent aminolysis followed by trimethylamine–borane reduction gave **25**. Acylation with pyruvoyl chloride converted the compounds **19** and **25** into the dioxopiperazines **28** and **29**, as well as the tetracyclic product **30** and **31**, respectively (Scheme V). Compound **29** was transformed into the didehydrodioxopiperazine **32**, an analogue of neoechinulin B (**7a**). The structure of **30** was determined by X-ray crystallographic analysis.

In recent years α-amino acid derivatives with a functionality in addition to the amino and carboxy groups have been shown to be characteristic structural elements of several naturally occurring compounds. There are indi-

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