Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.59; H, 8.29; N, 12.37.

Distillation of the last fractions yielded 1.2 g of a solid whose crystallization from ether–hexane or sublimation afforded colorless crystals of **4a**: mp 71–72.5°; ir (KBr) 4.45 μ (w, C≡N); pmr δ 3.96 (s, 4, oxymethylenes).

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.82; H, 8.02; N, 12.77.

Phthalimides 3c and 4c.—A solution of 500 mg of **3a** in 50 ml of dry ether was added over a 1-hr period to a stirring solution of 500 mg of lithium aluminum hydride in 50 ml of ether at room temperature and the mixture was stirred for 3 hr. Sodium sulfate decahydrate was added and the mixture was shaken and filtered. The salts were washed with methylene chloride and the combined filtrate and washings were evaporated. The residual liquid amine **3b**, 440 mg, had to be used for further reactions immediately, since it formed readily a carbon dioxide addition product. A solution of 45 mg of **3b** and 50 mg of phthalic anhydride in 3 ml of chloroform was refluxed for 30 min and then evaporated. The residue was heated at 220° (0.001 Torr) and sublimed in a fractional sublimator. Crystallization of the product, 50 mg, from ether–hexane yielded colorless crystals of **3c**: mp 166–168°; ir (KBr) 5.67 (m, C=O), 5.87 (s, C=O), and 6.20 μ (w, C=C).

Anal. Calcd for $C_{20}H_{24}O_4N_2$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.20; H, 6.64; N, 7.68.

The identical procedure was applied to **4a**. Crystallization of its imide from ether–hexane gave crystals of **4c**: mp 137–138°; ir (KBr) 5.65 (w, C=O), 5.86 (s, C=O), and 6.18 μ (w, C=C).

Anal. Calcd for $C_{20}H_{24}O_4N_2$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.67; H, 6.59; N, 7.82.

Diamines 5b and 6b and Their Derivatives.—A solution of 1.5 g of diamino ketal **4b** in 10 ml of 50% sulfuric acid was kept at room temperature for 18 hr. The solution was cooled, made alkaline with 5 *N* potassium hydroxide, and extracted exhaustively with methylene chloride. The extract was dried and concentrated to a 10-ml volume. Ethylene glycol, 25 ml, was added and the remaining methylene chloride was removed by distillation. Potassium hydroxide, 4.0 g, and 10 ml of 98% hydrazine were added and the mixture was heated at 190° for *ca.* 3 hr and subsequently refluxed under nitrogen for 12 hr. It was then cooled, acidified with 6 *N* hydrochloric acid, and evaporated under vacuum. The residue was dissolved in a minimum amount of 1 *N* potassium hydroxide and the alkaline solution was extracted with methylene chloride. The extract was dried and evaporated. Distillation of the residue gave 135 mg of **6b**, which had to be used immediately in the next reactions in view of its ready air oxidation and formation of a carbon dioxide adduct.

A solution of 50 mg of **6b** and 50 mg of phthalic anhydride in 1 ml of chloroform was refluxed in a sublimation tube for 30 min. It was evaporated and the tube was heated at 250° (0.005 Torr) in a fractional sublimator. Collection of a band of crystals gave 10 mg of solid whose crystallization from ether–hexane yielded colorless crystals of **6d**: mp 128–129°; mmp (with **6d** below) 127–128.5°; mmp (with **5d** below) 108–117°; ir (KBr) 5.66 (m, C=O), 5.85 (s, C=O), and 6.20 μ (w, C=C).

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.63; H, 7.53; N, 9.37.

The preparation of the 1-bromomethylquinolizidines **5c** and **6c** followed the procedure for the conversion of lupinine (**5a**) into optically active **5c**.[8] Epilupinine (**6a**), 330 mg, gave 410 mg of **6c**.

A solution of 100 mg of **5c** and 100 mg of potassium phthalimide in 4 ml of dry dimethylformamide was heated at 130° for 4 hr.[11] The mixture was cooled and evaporated. The residue was extracted with methylene chloride and chromatographed on 3 g of alumina (activity II). Elution with 50:1 ether–methanol gave 65 mg of a solid whose crystallization from ether–hexane yielded crystals of **5d**: mp 135–136°; ir (KBr) 5.66 (m, C=O), 5.87 (s, C=O), and 6.19 μ (w, C=C).

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.21; H, 7.62; N, 9.27.

A similar reaction with 40 mg of **6c** and 40 mg of potassium phthalimide gave 29 mg of **6d**: mp 127.5–129°; ir (KBr) identical with that of **6d** above.

Diamine **5b**, 1.4 g, was prepared from **3b**, 90 mg, by the procedure outlined above for the conversion of **4b** into **6b**. A solution of 35 mg of diamine **5b** and 35 mg of glutaric anhydride in 4 ml of chloroform was kept at room temperature for 2 hr. Evaporation of the solution and high vacuum distillation (bath temperature 250°) of the residue yielded 10 mg of liquid isolamprolobine (**7**): ir (CCl_4) 5.78 (m, C=O) and 5.95 μ (s, C=O).

A suspension of 232 mg of bromide **5c** and 135 mg of sodium glutarimide in 4 ml of dimethylformamide was refluxed for 2 hr. The mixture was cooled and filtered and the filtrate was evaporated. The residue was chromatographed on alumina (activity IV). Distillation of the 50:1 ether–methanol eluates yielded 40 mg of liquid **7** whose ir and pmr spectra and thin layer chromatographic behavior were identical with those of **7** above.

Lamprolobine (1).—The above procedure of conversion of **5b** into **7** was applied to 100 mg of **6b** and 100 mg of glutaric anhydride. It led to 30 mg of liquid *dl*-lamprolobine (1), ir (CCl_4) 5.78 (m, C=O) and 5.95 μ (s, C=O), identical in all respects with the spectrum of natural lamprolobine (1). Crystallization of its picrate from methanol gave yellow plates, mp 190–192°.

Anal. Calcd for $C_{21}H_{27}O_9N_5$: C, 51.11; H, 5.51; N, 14.19. Found: C, 51.45; H, 5.80; N, 14.12.

Registry No.—**1**, 22142-02-5; **2**, 22423-62-7; **3a**, 22423-63-8; **3c**, 22423-64-9; **4a**, 22423-65-0; **4c**, 22423-67-2; **5d**, 10248-22-3; **6d**, 22423-69-4; **1** picrate, 22142-03-6; 1-(3-ketobutyl)-3-cyanopyridinium bromide ethylene ketal, 22423-66-1.

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The Stereochemistry of (−)-Deoxynupharidine.[1] The Synthesis of (−)-(*R*)-α-Methyladipic Acid

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A recent publication[2] dealing with the synthesis of (+)-(*S*)-α-methyladipic acid has prompted us to disclose our synthesis of (−)-(*R*)-α-methyladipic acid, a synthesis carried out in an attempt to clarify the absolute configuration of (−)-deoxynupharidine and related Nuphar alkaloids.[3] Also reported here are nuclear magnetic resonance results which support the relative configuration of deoxynupharidine proposed earlier.

Originally, the absolute configuration of (−)-deoxynupharidine (1) was proposed on the basis that the (−)-α-methyladipic acid obtained on degradation (Scheme I) possessed the *S* configuration.[4] The configurational assignment of this acid was made on the basis of its synthesis from (−)-α-methyl-γ-butyrolactone, which in turn was correlated with (−)-(*S*)-methylsuccinic acid.[5] However, Turner[6] questioned

(1) Support of this work by the U. S. Department of Interior, Federal Water Pollution Control Administration and the McIntire–Stennis Cooperative Forestry Research Program of the U. S. Department of Agriculture is gratefully acknowledged.

(2) I. Kawasaki and T. Kaneko, *Bull. Chem. Soc. Jap.*, **41**, 1482 (1968).

(3) These include nupharidine, Δ^8-dehydrodeoxynupharidine, nupharamine, anhydronupharamine, nuphamine, and castoramine.

(4) (a) M. Kotake, I. Kawasaki, T. Okamoto, S. Matustani, S. Kusumoto, and T. Kaneko, *ibid.*, **35**, 1335 (1962); (b) Y. Arata and T. Iwai, *Kanazawa Daigaku Yakugakuba Kenkyu Nempo*, **12**, 39 (1962).

(5) T. Kaneko, K. Wakabayashi, and H. Katsura, *Bull. Chem. Soc. Jap.*, **35**, 1149 (1962).

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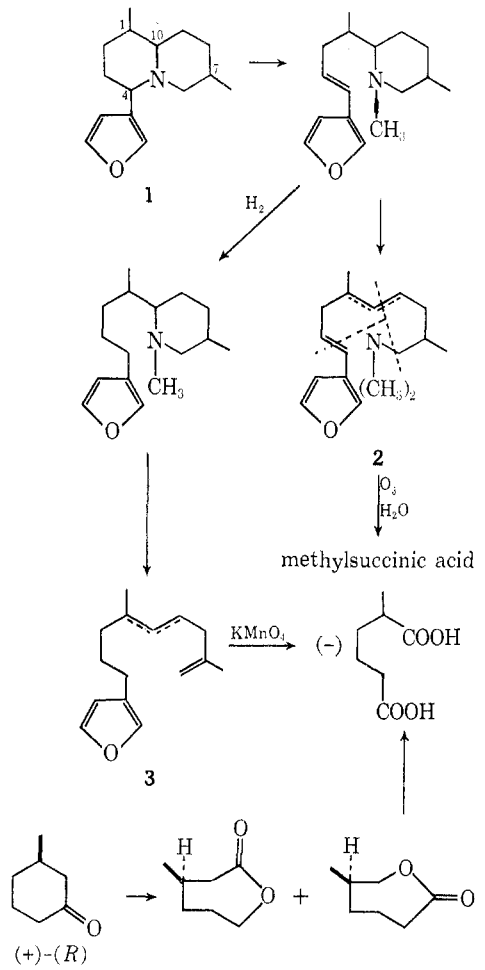


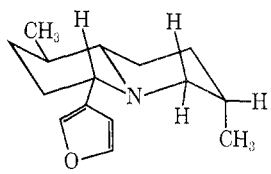
the assignment of the *S* configuration to (−)-α-methyladipic acid since (−)-(*R*)-α-methylglutaric acid, (+)-(*R*)-β-methyladipic acid, as well as (−)-α-methyladipic acid all were produced in the oxidative degradation of the cytochalasins A and B. Furthermore, Turner suggested that the proposed absolute configuration of (−)-deoxynupharidine should be reversed. Later, the formation of (−)-(*R*)-methylsuccinic acid by ozonolysis of the tertiary aminodiene **2** was offered[7] as experimental evidence to confirm Turner's suggestion.

We viewed an assignment of the absolute configuration of (−)-deoxynupharidine as ambiguous when based on a correlation with optically active methylsuccinic acid. The optically active acid possibly could have originated from C_{10}, C_1, C_2, and C_3, by ozonolysis of two carbon–carbon double bonds in **2**, or its antipode could have arisen from C_6, C_7, C_8, and C_9, by ozonolysis of a double bond and a carbon–nitrogen bond. There is precedent for the formation of aldehydes on ozonolysis of tertiary amines,[8] and oxidative conditions such as those used in the degradation of **2** would suffice to oxidize an aldehyde to a carboxylic acid. On the other hand, the origin of the (−)-α-methyladipic acid produced from **3** in the degradation is unequivocal and, therefore, a synthesis of (*R*)-α-methyladipic acid was justified for the purpose of correlation.

According to a known procedure,[9] (−)-(*R*)-δ-methyl-ε-caprolactone was obtained by repeated low-temperature fractional crystallization of the mixture of δ- and β-methyl-ε-caprolactones resulting from the Baeyer–Villiger oxidation of (+)-(*R*)-3-methylcyclohexanone (optical purity, 100%). Careful alkaline hydrolysis of the (−)-(*R*)-δ-methyl-ε-caprolactone and subsequent oxidation with an excess of potassium permanganate produced (−)-(*R*)-α-methyladipic acid which agreed in sign and magnitude of rotation with the (−) acid of degradation.

A convincing assignment of the relative configuration and conformation of (−)-deoxynupharidine has been made on the basis of synthetic methods and infrared studies.[10,11] Supporting evidence for the presence of one axial and one equatorial methyl group was furnished by an early nmr study,[4a] and a specific stereochemical assignment of methyl groups was made possible later by the transformation of nupharamine to deoxynupharidine and 7-epideoxynupharidine.[12] Since the 7 epimer was shown by nmr to have two equatorial methyl groups, deoxynupharidine must have C_1 equatorial and C_7 axial methyl groups. This stereochemistry is also demonstrated through examination of the C_6 protons in the 100 MHz nmr of deoxynupharidine. Both $H_{6\alpha}$ (7.30 τ) and $H_{6\beta}$ (8.12 τ) signals are identical quartets. The $H_{6\alpha}$ quartet arises from geminal (12.5 Hz) and equatorial–equatorial (6α–7β) coupling ($J_{e,e}$ = 2.5 Hz), while the $H_{6\beta}$ quartet arises from geminal (12.5 Hz) and axial–equatorial (6β–7β) coupling ($J_{a,e}$ = 2.5 Hz). These results are consistent with a structure having a C_7 axial methyl group. Therefore the C_1 methyl must be equatorial. Had the C_7 methyl been equatorial, a diaxial (6β–7α) coupling ($J \simeq 10$ Hz) would have resulted, in which case low- and high-field quartets would not be identical.

On the basis of the correlation of (−)-deoxynupharidine with (−)-(*R*)-α-methyladipic acid and the studies of relative stereochemistry, the absolute stereochemistry can be given as depicted in **4**.



4

Experimental Section

Spectra were obtained as follows: nmr in solution as indicated, 2% TMS (10 τ), Varian A-60A and Joelco HNM-4H-100, and determined by Mrs. D. Lee and Mrs. H. Jennison; ir in solution as indicated, Perkin-Elmer 137. Melting points were determined on a Kofler micro hot stage and are uncorrected; optical rotations, on a Perkin-Elmer 141 polarimeter. The elemental analysis was performed by Galbraith Laboratories.

(−)-(*R*)-α-**Methyladipic Acid.**—According to the method of Overberger and Kaye,[9] 10.3 g (0.0916 mol) of (+)-(*R*)-3-methyl-

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cyclohexanone,[13] $[\alpha]^{25}D$ +12.3° (1 dm, neat) [lit.[9] $[\alpha]^{27}D$ +12.01 (1 dm, neat)], was treated with a mixture of 26.5 g (0.126 mol) of trifluoroacetic anhydride and 3.63 g of 90% hydrogen peroxide to yield 9.4 g of colorless liquid (bp 83° at 2.5 mm) containing a mixture of δ-methyl-ε-caprolactone and β-methyl-ε-caprolactone. The nmr spectrum (CCl_4) of this mixture showed the low-field methylene signals at 5.84 (t, J = 4 Hz) and 6.0 (m, 4.5 Hz), which were assigned to the chemical shifts of the $-CH_2O-$ groups of β- and δ-methyl-ε-caprolactone, respectively. The δ-methyl-ε-caprolactone was isolated from the mixture by fractional crystallization at 0°, yielding 0.944 g of needles: mp 35.5–36.0°; $[\alpha]^{25}D$ −37.4° (c 0.855, $CHCl_3$) {lit.[9] $[\alpha]^{25}D$ −36.11 (c 0.46, $CHCl_3$)}; ir (CCl_4) 5.78 and 8.59 μ; nmr (CCl_4) τ 6.0 (m, 2 H, $-CH_2O-$), 7.47 (m, 2 H, $-CH_2C{=}O$), 8.20 (broad m, 5 H), and 9.08 (d, J = 6.8 Hz, 3 H).

A mixture of (−)-(*R*)-δ-methyl-ε-caprolactone (415 mg, 3.24 mmol), sodium hydroxide (372 mg), and 5 ml of aqueous ethanol was heated to reflux for 2 hr. Ethanol was removed by vacuum evaporation and the residue was treated with an excess of saturated potassium permanganate (about 1 g) until the pink coloration persisted. The mixture, after storing at room temperature overnight, was treated with a few crystals of sodium bisulfite until the decantation was colorless. The brown precipitate was removed by filtration and the filtrate was extracted twice with 50 ml of methylene chloride. The aqueous layer was separated and adjusted to pH 1 by adding concentrated hydrochloric acid. Continuous extraction with ether yielded 472 mg of crystals, mp 75–78°. Fractional crystallization (thrice) from a mixture of ether and petroleum ether afforded 246 mg of crystals: mp 81–82°; $[\alpha]^{25}D$ −13.4° (c 2.15 EtOH); ir ($CHCl_3$) 3.80 (br) and 5.85 μ (s) (COOH); nmr ($CDCl_3$) τ −1.6 (s, 2 H, COOH), 7.62 (m, 3 H), 8.33 (m, 4 H), and 8.78 (d, J = 7 Hz, 3 H).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.47; H, 7.55. Found: C, 52.39; H, 7.50.

(+)-S-α-Methyladipic acid had lit.[2] mp 81–83°, $[\alpha]^{25}D$ +13.8° (c, 1.91 in EtOH). (−)-α-Methyladipic acid had lit.[4b,6] mp 82–83°, $[\alpha]^{28}D$ −18°.

(−)-Deoxynupharidine.—A 200-mg sample of nupharidine ($[\alpha]D$ +14.8° mp 218–224°, hydrochloride mp 228°; lit.[14] $[\alpha]D$ +13.0, mp 212°, hydrochloride mp 196°) was dissolved in 100 mg of absolute ethanol, and 100 mg of 10% palladized charcoal was added. The mixture was shaken under 1 atm of hydrogen at room temperature. After 0.5 hr, consumption of hydrogen was complete. The catalyst was filtered and the filtrate evaporated. Chromatography of the 190 mg of oily residue on neutral alumina (activity II), using hexane (95%)–ether (5%) gave 178 mg of deoxynupharidine: $[\alpha]^{25}D$ −105° (48.6 mg in 2 ml of MeOH), mp (hydrochloride salt) 268°; lit.[15] $[\alpha]^{25}D$ −112.5°, mp (hydrochloride salt) 262°. The key features of the 100-MHz nmr ($CDCl_3$) spectrum are given in Table I.

TABLE I

100-MHz NMR SPECTRUM OF DEOXYNUPHARIDINE

Chemical shift rel to TMS, (τ 10)	No. of protons	Splitting pattern, J, Hz	Assignment[b]
9.01	6	Doublet, 7.0	C_7 CH_3 (ax)
9.08		Doublet, 5.6	C_1 CH_3 (eq)
8.12	1/2[a]	Quartet, 12.5, 2.5	$C_{6\beta}$ H (ax)
7.30	1	Quartet, 12.5, 2.5	$C_{6\alpha}$ H (eq)
7.12	1	Quartet, 8.0, 6.2	$C_{4\beta}$ H (ax)

[a] Only the lower field half of the 8.12 quartet is clearly observed. The high-field portion is superimposed on the envelope of the remaining methinyl and methylene protons. [b] ax = axial, eq = equatorial.

Registry No.—4, 1143-54-0; (−)-(*R*)-α-methyladipic acid, 16200-25-2.

(13) Purchased from the Aldrich Chemical Co.

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Anomeric Methyl 4-Thio-D-arabinofuranosides[1]

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Since some nucleosides of D-arabinose possess antitumor activity,[3] and a number of thio and amino sugars and their derivatives have been shown to have biological activity, it is of interest to prepare nucleosides of 4-thio-D-arabinose. The conversion of 9-(4′-thio-β-D-xylofuranosyl)adenine into 9-(4′-thio-β-D-arabinofuranosyl)adenine has been reported,[4] but the synthesis is not applicable to other nucleosides. This paper describes the synthesis of the anomeric methyl 4-thio-D-arabinofuranosides, making the sugar analog available for incorporation into a variety of nucleosides.

The starting material used in the synthesis is 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose,[5] an intermediate prepared earlier in this laboratory for the synthesis of 5-thio-D-glucopyranose. Selective hydrolysis of the isopropylidene group in the presence of the thiolacetate group of 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I) in 50% aqueous acetic acid at 70° gives a 78% yield of crystalline 5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II) and a 16.2% yield of 3,6-di-*O*-benzyl-5-thio-D-glucopyranose (III) Scheme (I).

The structure of compound III is confirmed by the absence of absorptions at 1685 (*S*-acetyl) and 2550 cm^{-1} (SH). Also, the absence of resonance signals at τ 7–7.2 (SH), 7.76 (*S*-acetyl), and 8.5–8.7 (isopropylidene) indicates that in compound III sulfur has replaced oxygen as the heteroatom in a stable pyranose ring. The strong dextrorotation of compound III (+97.5°) compared with the dextrorotations of compounds I and II (−64.3[5] and −40°) having furanose structures suggests that compound III has a stable pyranose structure in which sulfur has entered the ring. The presence of the *S*-acetyl group in compound II is confirmed by an absorption at 1685 cm^{-1} and by a resonance signal in the nmr spectrum at τ 7.76. The absence of a signal in the region of τ 8.5–8.7 confirms the absence of the isopropylidene group. Compound II is further characterized by acetylation to obtain 1,2-di-*O*-acetyl-5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (IX) for which both the ir and nmr spectra showed the presence of *S*-acetyl and *O*-acetyl groups.

The structure of compound III is confirmed by the absence of an absorption at 1685 cm^{-1}. Also, the absence of a resonance signal at τ 7.76 (*S*-acetyl protons) and τ 8.5–8.7 (isopropylidene protons) further indicates that in compound III sulfur has replaced the oxygen as the heteroatom in a stable pyranose ring.

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(2) National Institutes of Health predoctoral fellow, 1965–1968.

(3) For a review see S. S. Cohen in "Progress in Nucleic Acid Research and Molecular Biology," Vol. 5, J. N. Davidson and W. E. Cohn Ed., Academic Press Inc., New York, N. Y., 1965, p 1.

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