from neutron diffraction data[4] indicates a definite steric interaction between the C-4 methyl protons and H-3, whereas no such interaction exists between H-2 and H-1. Since it is well known that such steric interaction causes an upfield shift in resonances of interacting ^{13}C nuclei, the high field signal at 55.3 is assigned to C-3 while the lower field absorption at 59.5 to C-2.

The above methodology employed for the cmr spectral analysis will be particularly useful in the structure elucidation of other new, structurally related melampolides and complex natural products in general. After accumulating data from other sesquiterpene lactones we hope to correlate the ^{13}C chemical shift data with stereochemical and conformational features of the melampolides. The availability of accurate conformational information of melampolides in solution will help to better understand the biogenesis of these highly strained medium rings. Furthermore, the newly obtained data will be used extensively in our biochemical systematic studies of the three white-rayed species of the genus *Melampodium*.[2,8]

Experimental Section

The nmr spectral data were obtained on a Varian XL-100-15 spectrometer operating Fourier transform mode with proton decoupling. Data were accumulated in a Varian 620F computer using 5000-Hz sweep width in 8192 points. Data acquisition and pulse delay times were 0.8 and 0.9 sec. The number of pulses (transients) employed were varied and are recorded on respective cmr traces. Melampodin (300 mg) dissolved in 2 ml of $CDCl_3$ was employed for the nmr study. The chemical shifts are relative to internal tetramethylsilane and are estimated to be accurate to ±0.04 ppm.

Acknowledgment is made to the University Council on Research, Louisiana State University, for partial support of this work. We thank Dr. T. F. Stuessy for collecting and authenticating the plant collections.

Registry No.—Melampodin, 35852-26-7.

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Nucleosides. LXXXIV. Total Synthesis of Pentopyranine C, a Nucleoside Elaborated by *Streptomyces griseochromogenes*[1]

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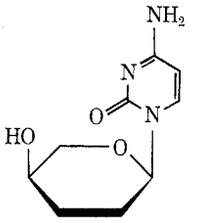
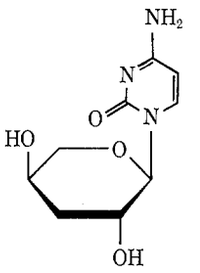
Received April 18, 1973

Recently, Seto, *et al.*,[2] isolated two cytosine nucleosides, pentopyranine A and C, from the fermentation broth of *Streptomyces griseochromogenes*, the blasticidin S-producing microorganism.[3] The structures of these nucleosides were given as 1-(2,3-dideoxy-α-L-*glycero*-pentopyranosyl)cytosine (**1**) and 1-(3-deoxy-α-L-*threo*-pentopyranosyl)cytosine (**2**). Pentopyranine A and C are therefore the first naturally occurring nucleosides possessing the α-L configuration.



1, pentopyranine A



2, pentopyranine C

We now report the total synthesis of pentopyranine C (**2**) and its furanosyl isomer (**13**) by condensation of bis(trimethylsilyl)-N^4-acetylcytosine with tri-*O*-acetyl-3-deoxy-L-*threo*-pentoses (**9** and **10**) in the presence of stannic chloride.[4]

The starting material, 3-deoxy-1,2-*O*-isopropylidene-α-L-*threo*-pentose (**6**), was prepared by the procedure of Prokop and Murray[5] as shown in Chart I from 3-deoxy-di-*O*-isopropylidene-α-D-*xylo*-hexofuranose (**3**).[5,6] Acid hydrolysis of **6** afforded the aldopentose (**8**) which was acetylated to give a mixture of **9** and **10**. This mixture of triacetates (**9** and **10**) was not separated, but condensed directly with bis(trimethylsilyl)-N^4-benzoylcytosine to afford the mixture **11a** and **12a**, which was saponified and acetylated to **11b** and **12b**. The latter mixture was separated easily by fractional crystallization from methanol. The physical constants (melting point, uv, ir, and nmr) of **11b** were identical with those reported[2] for the triacetyl derivative of pentopyranine C. After deacetylation of **11b**, a product (**2**) was obtained which was identical with pentopyranine C with respect to melting point, optical rotation, and uv, ir spectral characteristics.

The structure of compound **12b** was established by an unambiguous synthesis. Acetylation of **6** gave compound **7** which was acetolyzed to the triacetate (**9**). Condensation of **9** with bis(trimethylsilyl)-N^4-acetylcytosine gave a nucleoside identical in all respects with **12b**. After deacetylation of **12b**, the free nucleoside (**13**) was obtained. The α-L configuration for **13** was established by comparison of its ORD curve (in water) with that of 1-(α-L-arabinofuranosyl)cytosine (**14**).[7] Both **13** and **14** showed positive Cotton effects with two extrema at 273 and 218 mμ (the amplitudes being 180 and 230, respectively).

The total synthesis of pentopyranine C provides conclusive proof of the structure of this natural product which is believed to be a shunt pathway product[2] in the synthesis of the important anti rice blast disease agent, Blasticidin S.[3]

Experimental Section

Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

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(6) T. Chiu, K. A. Watanabe, and J. J. Fox, *Carbohyd. Res.*, in press.

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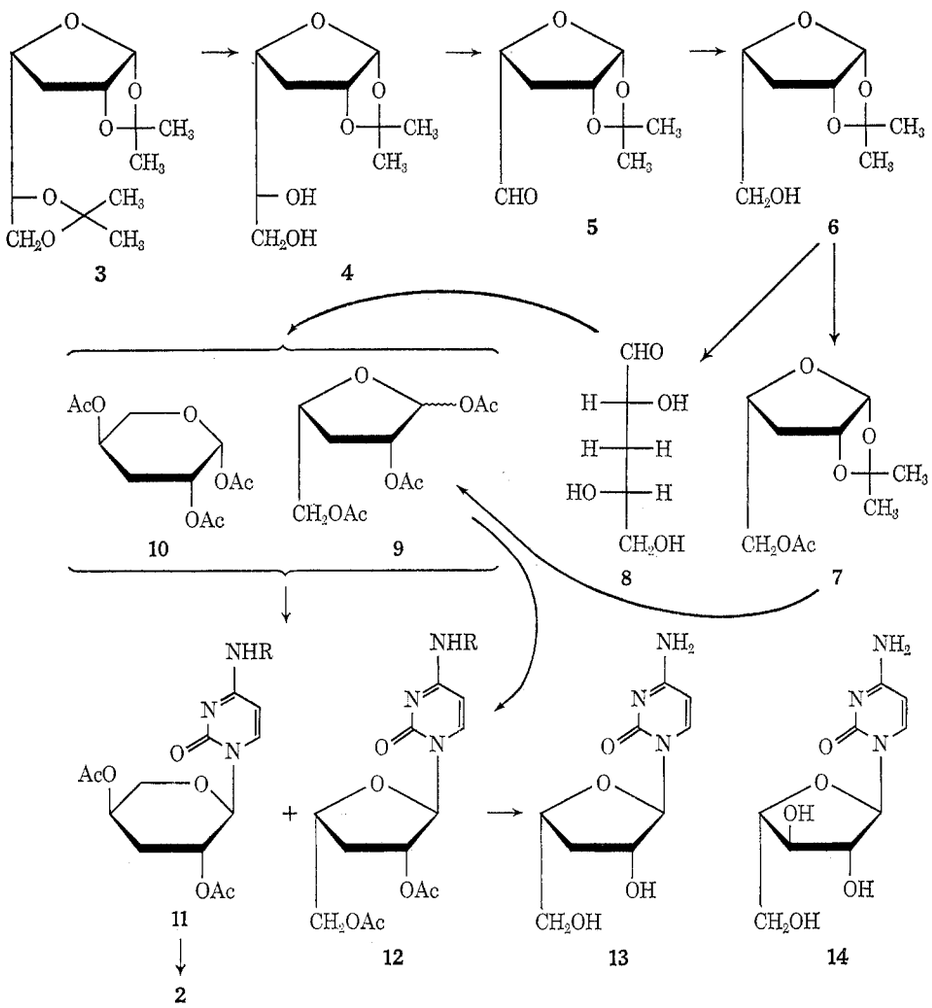
CHART I



a, R = Bz
b, R = Ac

3-Deoxy-L-*threo*-pentose (8).—A mixture of compound **6** (7.0 g) and Dowex 50 (H^+) (~5 ml) in water (70 ml) was stirred for 1.5 hr. The resin was filtered, and the filtrate was concentrated to a syrup (5.0 g) which was free of isopropylidene group (nmr). This product was not characterized further, but used directly in the next step.

Tri-*O*-acetyl-3-deoxy-L-*threo*-pentofuranose (9) and -β-L-*threo*-pentopyranose (10).—Compound **8** (5.0 g) was acetylated in pyridine (26 ml) and acetic anhydride (20 ml) overnight. The mixture was poured into ice–water (300 ml) and extracted with dichloromethane (5 × 60 ml). The organic extracts were washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate, and condensed to dryness. The residue was coevaporated several times with toluene. The nmr spectrum in $CDCl_3$ showed that the product consists mainly of **9** and **10** about 1:1 ratio (H-1 for **9**, δ 6.19, singlet; H-1 for **10**, δ 5.78, doublet $J_{1,2} \cong 3.5$ Hz). This product was used directly in the next step.

1-(2,4-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentopyranosyl)-N^4-acetylcytosine (11b) and 1-(2,5-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentofuranosyl)-N^4-acetylcytosine (12b).—To a solution of the above mixture of **9** and **10** (4.5 g) and tin tetrachloride (8 ml) in 1,2-dichloroethane (250 ml) was added a 1,2-dichloroethane solution (100 ml) of bis(trimethylsilyl)-N^4-benzoylcytosine[8] prepared from 12 g of N^4-benzoylcytosine. The mixture was stirred overnight at room temperature and then poured into a cold, saturated sodium bicarbonate solution (400 ml). The organic layer was washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was crystallized from ethanol. Compounds **11a** and **12a** cocrystallized. Both **11a** and **12a** had identical mobilities on tlc in several solvent systems.

The mixture of **11a** and **12a** (4.2 g) was treated with methanolic ammonia saturated at 0° (~120 ml) overnight. After evaporation, the residue was partitioned between water and ether (50 ml each). The organic layer was washed with chloroform (2 × 50 ml) and evaporated to give a mixture of **2** and **13** as a glass. All attempts to separate **2** and **13** by fractional crystallization or column chromatography failed.

The mixture of **2** and **13** (1 g) was dissolved in pyridine (5 ml) and acetylated with acetic anhydride overnight. The mixture was poured into ice–water (60 ml) and extracted with chloroform (2 × 50 ml). The combined extracts were washed with water, saturated sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residue was coevaporated several times with ethanol to remove traces of pyridine and then dissolved in methanol (~5 ml), and the mixture was kept at 0° overnight. Compound **12b** (180 mg) crystallized as needles: mp 179–181°; $[\alpha]^{27}D$ +43° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$, TMS internal standard) OAc δ 2.17 (6 H), NAc 2.27 (3 H), H-5′,5″ 4.2 (doublet, 2 H), H-4′ 4.83 (multiplet), H-2′ 5.58 (multiplet), H-1′ 5.87 (doublet $J_{1',2'} = 1.5$ Hz).

Anal. Calcd for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.42; N, 11.89. Found: C, 51.05; H, 5.60; N, 11.83.

The mother liquor of crystallization of **12a** was kept at 0° for 2 days. Compound **11b** (121 mg) crystallized as cubes: mp 204–205° (lit.[2] mp 203–205°); $[\alpha]^{27}D$ 0° (*c* 1.0, $CHCl_3$); nmr ($CDCl_3$; TMS internal standard) OAc δ 1.96 (3 H), 2.16 (3 H), NAc 2.28 (3 H), H-5′,5″ 4.01 (2 H, quartet $J_{5',5''} \cong 13.0$ Hz), H-4′ 5.11 (narrow multiplet), H-2′ 5.29 (broad multiplet), H-1′ 5.91 (doublet $J_{1',2'} = 9.5$ Hz), H-5, H-6 7.51 and 7.82 (doublets $J_{5,6} = 7.5$ Hz).

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1-(3-Deoxy-α-L-*threo*-pentopyranosyl)cytosine (2) (Pentopyranine C).—Compound **11b** (98 mg) was treated overnight with methanolic ammonia (~10 ml) saturated at 0°. After evaporation of the solvent, the residue was triturated with ether (2 × 10 ml) and chloroform (2 × 10 ml), and the residue was crystallized from ethanol to give compound **2**: 49 mg; mp 144–145°; $[\alpha]^{27}D$ +19° (*c* 1.0, H_2O) (lit.[2] mp 143–145°, $[\alpha]^{21}D$ +20°).

1-(3-Deoxy-α-L-*threo*-pentofuranosyl)cytosine (13).—Compound **12a** (110 mg) was deacetylated with methanolic ammonia as described for the synthesis of **2** from **11a**. Compound **13** (42 mg) was obtained as needles after recrystallization from methanol: mp 160–163°, $[\alpha]^{27}D$ +19° (*c* 1.0, H_2O).

Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.43; H, 5.66; N, 18.20.

5-*O*-Acetyl-3-deoxy-1,2-di-*O*-isopropylidene-β-L-*threo*-pentose (7).—Compound **6**[5] (5 g) was acetylated in pyridine (20 ml) with acetic anhydride (5 ml) overnight. The crude acetyl derivative **7** (5 g) was obtained as a syrup which was chromatographically homogeneous and sufficiently pure for the next step.

Tri-*O*-acetyl-3-deoxy-β-L-*threo*-pentofuranose (9).—To a cooled and stirred solution of **7** (5 g) in acetic acid (20 ml) and acetic anhydride (10 ml) was added sulfuric acid (1 ml). The mixture was kept overnight at room temperature, then partitioned between dichloromethane (100 ml) and ice–water (100 ml). The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 100 ml), water, dried over sodium sulfate, and evaporated to dryness. The residue was coevaporated several times with toluene to remove traces of acetic acid. This syrup was contaminated with a small amount of the α anomer: nmr ($CDCl_3$, TMS internal standard) β-H-1 δ 6.18 (singlet), α-H-1 6.80 (doublet, $J_{1,2}$ = 3.5 Hz). No anomeric signal corresponding to the pyranose isomers was detected by nmr.

1-(2,5-Di-*O*-acetyl-3-deoxy-α-L-*threo*-pentofuranosyl)cytosine (12b).—The anomeric mixture of **9** was condensed with bis(trimethylsilyl)-N^4-acetylcytosine[8] (prepared from 5 g of N^4-acetylcytosine) in 1,2-dichloroethane (250 ml) in the presence of stannic chloride (8 ml). Compound **12b** (2.2 g) was obtained after two recrystallizations from methanol: mp 179–181°, $[\alpha]^{27}D$ +43° (*c* 1, $CHCl_3$). A mixture melting point of this sample with **12b** prepared as described previously in this paper was undepressed. Ir and nmr spectra of both samples were identical.

Registry No.—**2**, 39007-97-1; **7**, 41107-64-6; **8**, 41107-43-1; **9**, 41107-68-0; **10**, 41164-55-0; **11b**, 41164-56-1; **12b**, 41164-57-2; **13**, 41164-58-3.

Conversion of 1,2-*O*-Isopropylidene-α-D-xylofuranose into 3-*O*-Benzoyl-5-bromo- and -5-iodo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose *via* a Cyclic *N,N*-Dimethylbenzamide Acetal Derivative

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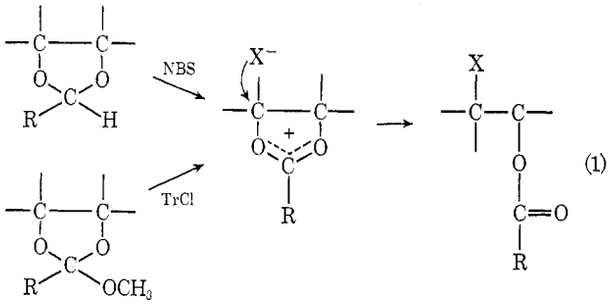
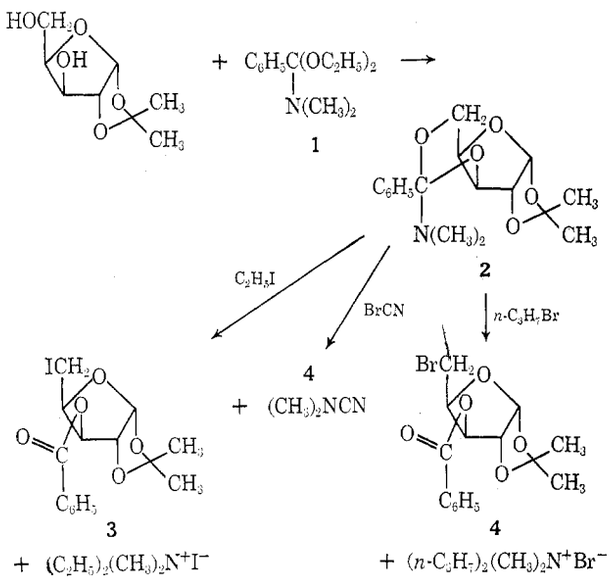
Received March 27, 1973

We wish to report a new method for converting glycols into esters of halohydrins under very mild conditions requiring no acid or base catalyst. Previously, cyclic benzylidene acetals of carbohydrates have been opened with *N*-bromosuccinimide to form bromodeoxy benzoate derivatives.[1] For example, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was converted into methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside. Recently, it has been reported that acetates of simple aliphatic chlorohydrins are readily prepared by the reaction of cyclic ortho esters with trityl chloride.[2] Both of these reactions are regioselective and stereospecific and it has been proposed that they proceed by a nucleophilic attack by halide ion on an acyloxonium ion intermediate (eq 1).



The dimethyl acetal of *N,N*-dimethylbenzamide is reported to react with methyl β-D-ribofuranoside to give a 2,3-cyclic amide acetal derivative.[3] We have found that 1,2-*O*-isopropylidene-α-D-xylofuranose reacts on standing with a dichloromethane solution of *N,N*-dimethylbenzamide diethyl acetal **1** to give 3,5-*O*-[α-(dimethylamino)benzylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**2**). The compound, isolated by distillation, slowly crystallized after standing a few weeks at room temperature and was recrystallized from pentane, mp 74–75.5°. Gas chromatography showed only one peak, but the nmr spectrum indicated the presence of two compounds. Three singlets for the *C*-methyls (δ 1.33, 1.43, and 1.50), two singlets for *N*-methyl (2.07 and 2.27, ratio of 6:1), and two doublets for the C-1 hydrogen (5.97 and 6.07) suggested two isomers differing only in the chirality of the benzyl carbon atom.

When **2** was refluxed with methyl or ethyl iodide a quaternary ammonium iodide salt precipitated. Evaporation of the filtrate gave a colorless syrup (**3**): $C_{15}H_{17}IO_5$. The ir spectrum (liquid film) showed absorption at 1727 cm^{-1}, indicative of a benzoate ester. The nmr spectrum was compatible with 3-*O*-benzoyl-5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose. A two-proton doublet appeared at δ 3.33 ($J_{4,5}$ = 7 Hz) upfield from a one-proton doublet at 5.58 ($J_{3,4}$ = 3 Hz, $J_{2,3}$ = 0); consequently the iodine substitution was assigned



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