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SYNTHESIS OF DEOXYPOLYOXIN C, " THYMINE POLYOXIN C "[*1]

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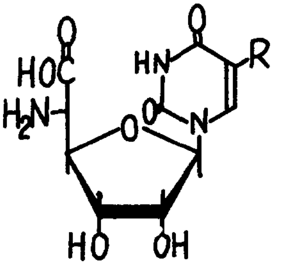
Polyoxins, a mixture of novel antifungal agents produced by Streptomyces cacaoi var. asoensis, were recently determined by K. Isono et al[2] to have a new class of α-amino acid nucleoside, 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)-pyrimidines (I), as a basic component. The synthesis of a fully protected sugar component of I was reported by Naka et al[3] and very recently the conversion of uridine to Uracil Polyoxin C (II) has been announced by J. G. Moffatt et al[4]. We now describe the synthesis of 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)thymine " Thymine Polyoxin C " (III).

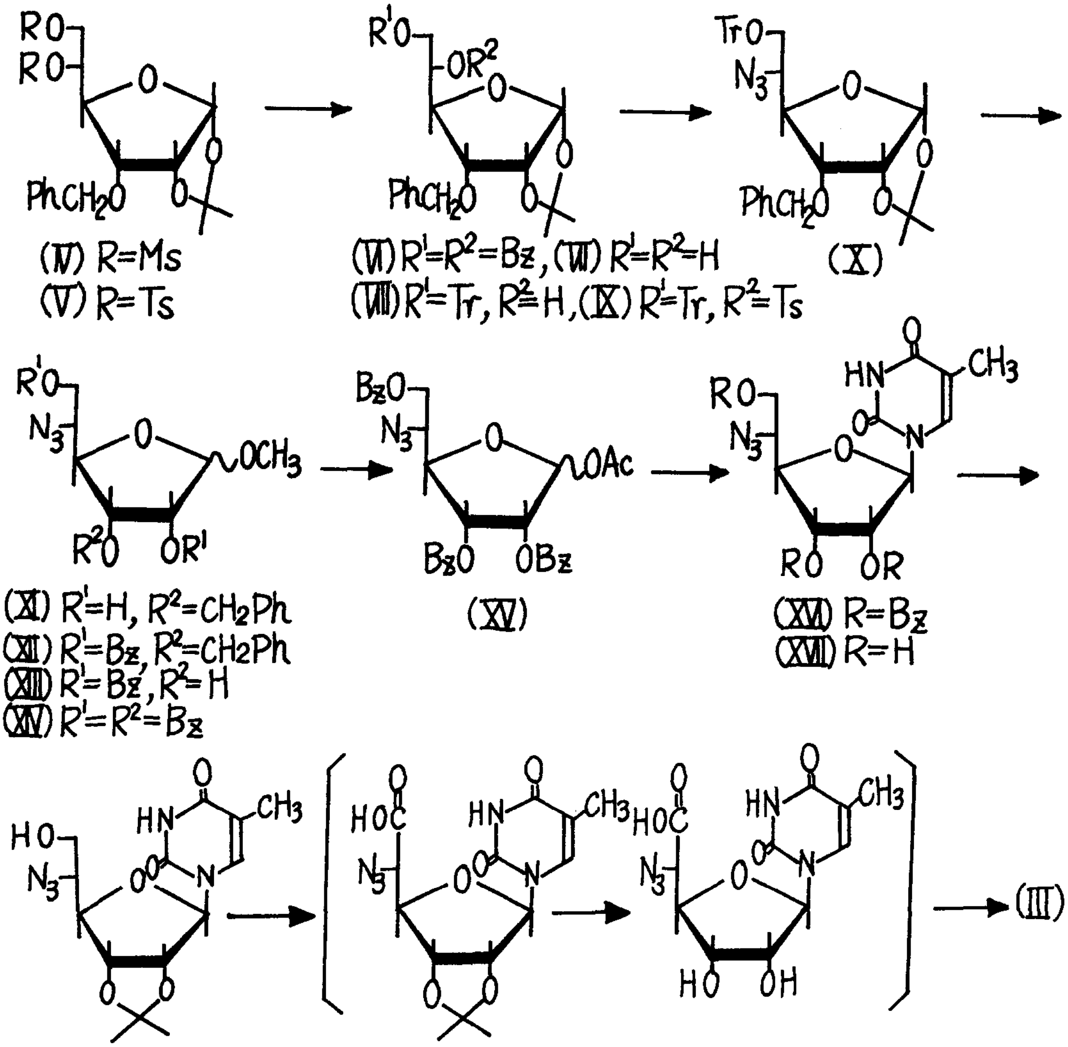
Treatment of 3-O-benzyl-1,2-O-isopropyridene-5,6-di-O-methanesulfonyl-α-D-allofuranose (IV)[5] or 3-O-benzyl-1,2-O-isopropylidene-5,6-di-O-p-toluenesulfonyl-α-D-allofuranose (V)[**], $[\alpha]_D^{22}$+40° (c 0.35, $CHCl_3$), with an excess of sodium benzoate containing a little benzoic anhydride in HMPT (hexamethylphosphoric triamide) gave in good yield 5,6-di-O-benzoyl-1,2-O-isopropylidene-β-L-talofuranose (VI), $[\alpha]_D^{19}$ +29° (c 0.12, $CHCl_3$), λ_{max}^{film} 1730 ($O\overset{O}{C}C_6H_5$) cm^{-1}, with an inversion at C-5. Alkaline hydrolysis of the ester group of VI with methanolic KOH afforded VII, which was tritylated to 6-O-tritylate (VIII), m.p. 115-6°; $[\alpha]_D^{23}$ +33° (c 0.24, $CHCl_3$); λ_{max}^{KBr} 3500 (OH) cm^{-1}. Tosylation of VIII gave 3-O-benzyl-1,2-O-isopropylidene-5-O-tosyl-6-O-trityl-β-L-talofuranose (IX), $[\alpha]_D^{22}$ +14° (c 0.11, $CHCl_3$). Treatment of IX with sodium azide in HMPT for 4 hr at 80° gave in good yield 5-azido-3-O-benzyl-5-deoxy-1,2-O-isopropylidene-6-O-trityl-α-D-allofuranose (X), m.p. 140°; $[\alpha]_D^{23}$ +20° (c 0.20, $CHCl_3$); λ_{max}^{KBr} 2150 (N_3) cm^{-1}. Methanolysis of X with 3% methanolic hydrogen chloride at room temperature overnight afforded an anomeric mixture of methyl 5-azido-3-O-benzyl-5-deoxy-D-allofuranoside (XI), λ_{max}^{film} 3500 (OH), 2150 (N_3), which was benzoylated to 2,6-di-O-benzoate (XII), λ_{max}^{film} 2100



(I)

(II) R=H, (III) R=CH_3

Bz=Benzoyl
$PhCH_2$=Benzyl
Ts=p-Toluenesulfonyl
Ms=Methanesulfonyl
Tr=Trityl
Ac=Acetyl



(IV) R=Ms
(V) R=Ts

(VI) $R^1=R^2=Bz$, (VII) $R^1=R^2=H$
(VIII) $R^1=Tr$, $R^2=H$, (IX) $R^1=Tr$, $R^2=Ts$

(X)

(XI) $R^1=H$, $R^2=CH_2Ph$
(XII) $R^1=Bz$, $R^2=CH_2Ph$
(XIII) $R^1=Bz$, $R^2=H$
(XIV) $R^1=R^2=Bz$

(XV)

(XVI) R=Bz
(XVII) R=H

(XVIII)

(XIX)

(XX)

(N_3), 1735 ($O\overset{O}{C}C_6H_5$) cm^{-1}.

The removal of the benzyl protecting group of XII without reduction of the azido group was one of the key steps in the synthesis of III. Compound XII was treated with excess boron trichloride in dry dichloromethane[6] under cooling with dry ice-acetone for 30 hr and the excess boron trichloride was decomposed by adding a large amount of absolute methanol below -20° and then the solution was neutralized with $NaHCO_3$. After the inorganic material was filtered off, the solvent was evaporated in vacuo to give in 85% yield an anomeric mixture of methyl 5-azido-2,6-di-O-benzoyl-5-deoxy-D-allofuranoside (XIII), λ_{max}^{film} 3520 (OH), 2100 (N_3), 1730 ($O\overset{O}{C}C_6H_5$) cm^{-1}. Benzoylation of XIII afforded 2,3,6-tri-O-benzoate (XIV), which was treated with a mixture of acetic acid, acetic anhydride, and sulfuric acid overnight at room temperature to give 1-O-acetyl-5-azido-2,3,6-tri-O-benzoyl-5-deoxy-D-allofuranose (XV), λ_{max}^{film} 2100 (N_3), 1740,1735 ($O\overset{O}{C}R$), 1610, 1590 (C_6H_5) cm^{-1}, δ ($CDCl_3$) 2.08, 2.15 (acetates of α and β).

Treatment of XV with 5-methyl-2,4-bis(trimethylsiloxy)pyrimidine[7] in 1,2-dichloromethane in the presence of stannic chloride[8] overnight at room temperature afforded almost quantitatively[9] 1-(5-azido-2,3,6-tri-O-benzoyl-5-deoxy-β-D-allofuranosyl)thymine (XVI), m.p. 199-200°, $[\alpha]_D^{25}$ -44.5° (c 0.7, DMSO); λ_{max}^{KBr} 3300(NH), 2100 (N_3), 1730,1720,1690 (CO) cm^{-1}; δ (DMSO-d_6) 8.02-7.30 (15H, protons on benzene ring), 7.45 (s, H-6), 2.83 (3H, s, CH_3-5) ppm. Treatment of XVI with sodium methoxide in emthanol gave 1-(5-azido-5-deoxy-β-D-allofuranosyl)thymine (XVII), m.p. 141.5-2.5°; $[\alpha]_D^{22}$ -15° (c 0.07, pyridine); λ_{max}^{KBr} 3500-3200 (OH), 3050 (NH), 2100 (N_3), 1720,1690,1680, 1660 (CO) cm^{-1}: δ (DMSO-d_6) 7.49 (1H, s, H-6), 5.78(1H, d, $J_{1',2'}$5.1Hz, H-1'), 4.16 (2H, m), 3.80 (2H, m), 3.65 (2H, m), 2.82 (3H, s, CH_3-5) ppm. Compound XVII was acetonized by treating with 2,2-dimethoxy propane in acetone in the presence of p-toluenesulfonic acid to give in good yield 1-(5-azido-5-deoxy-2,3-O-isopropylidene-β-D-allofuranosyl)thymine (XVIII), m.p. 158-159°; $[\alpha]_D^{25}$ -13.2° (c 0.24, pyridine); λ_{max}^{KBr} 3550 (OH), 3270 (NH), 2150 (N_3), 1730,1720, 1700, 1690 (CO) cm^{-1}; δ (DMSO-d_6) 7.52 (1H, s, H-5), 5.82(1H, d, $J_{1',2'}$2Hz, H-1'), 1.84 (3H, s, CH_3-5), 1.52 and 1.34 (two 3H, two s, isopropylidene group)ppm.

The final three steps of reactions (CrO_3 oxidation, deisopropylidenation, and catalytic reduction) were carried out without characterization of the products.

Compound XVIII was oxidized with CrO_3 in absolute acetic acid[10] for 2 days at room temperature. After purification by column chromatography on silicic acid, 5-azido-D-alluronic acid derivative (XIX) was obtained (40%). It was treated with 80% formic acid overnight at room temperature to give XX. Catalytic reduction of the azido group of XX over 10% Pd-C afforded almost quantitatively 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)thymine (III), m.p. 242-4° (dec), $[\alpha]_D^{25}$ +8.2° (c 0.7, H_2O); lit.[2] m.p. 240-4° (dec), $[\alpha]_D^{22}$ +8.7° (c 0.2, H_2O). Its IR spectrum t.l.c., and electrophoretic properties completely agreed with those of the authentic III.

The above synthetic method is of general applicability to the synthesis of other natural polyoxins and purine analogs of polyoxin nucleosides and the results of the related studies will be reported in near future.

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REFERENCES AND FOOTNOTES

* Syntheses with Azido Sugars Part IV.

** All new compounds gave the satisfactory results of the elemental analyses.

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