Synthesis of some new C-nucleosides from L-arabinose and D-glucose

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Dedicated to Professor Ahmed Fathy Sayed Ahmed, Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt

Abstract

The reaction of L-arabinose with malonitrile yielded oxazoline **1**, which on reaction with thioglycolic acid and acetyl chloride afforded the 4-oxothiazolyl *β*-L-arabinfurano oxazoline **(2**) and 1-cyanomethylcarboxamido-2-chloro-*β*-L-arabinose **(3),** respectively. The reaction of compound **(1)** with benzaldehyde led to the formation of oxazoline **(4),** which was reacted with cyanoacetamide to give compound **(5)**. After treatement of glucose with phenylhydrazine, the compound was reacted with diethylmalonate to give the pyrazole derivative **(7)**. The biological activity of the prepared compounds was investigated.

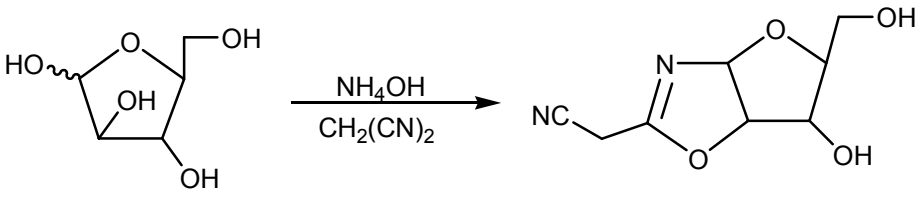
Keywords: L-Arabinose, thioglycolic

Introduction

The synthesis of modified nucleosides has recently received considerable attention in search for compounds with antiviral and anticancer activity.[1] Moreover, a class of nucleosides with the unnatural L-configuration has recently drawn considerable attention of medicinal chemists due to their unique potency and toxicity profile.[2-6] Several compounds comprising a 1,3,4-oxadiazole nucleus exhibit various biological activities such as antifungal, [7,8] anti-inflammatory,[9] antibacterial,[10] anticonvulsive,[11] and serotonin antagonist activity.[12] Furthermore, the synthesis[13,14] of *C*-nucleosides and their acyclic[15,16] analogues received also attention of many investigators due to their documented biological activities.[17] Sugar moieties linked to these structures would enhance their penetration into cells and therefore, contribute to their activities.

Results and Discussion

L-Arabinose was used as starting material for the preparation of modified nucleosides. Thus, treatment of L-arabinose with malonitrile in the presence of ammonium hydroxide in methanol gave compound **1.**



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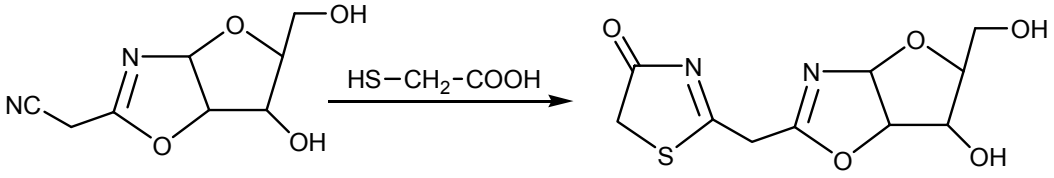
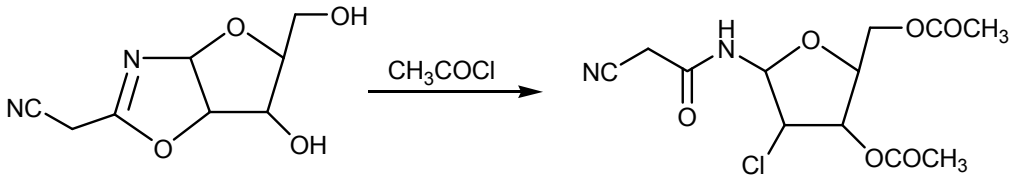
Subsequent, treatment of compound **1** with thioglycolic acid in the presence of benzene gave 2-methyl-4-oxothiazolyl *β*-L-arabinfurano [1`, 2`:4, 5] oxazoline **2.**



1 **2**

The structure of **2** was established on the basis of its elemental analysis and spectral data. The mass spectrum of **2** showed the molecular ion peak M^+ at (m/z: 272) supporting the molecular formula $C_{10}H_{12}N_2O_5S$. The fragmentation in the mass spectrum showed a peak at m/e (208, 25.3%) and m/e at (176, 25.4%).

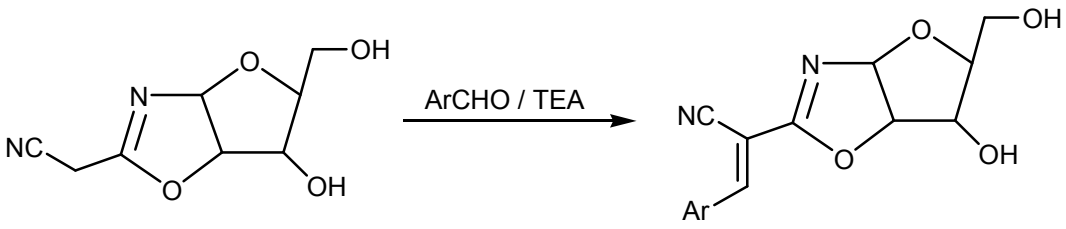
Opening of the oxide bridge of compound **1** with the introduction of a chlorine atom at the C-2 position of compound **1** was accomplished using acetyl chloride in anhydrous acetonitrile to afford 1-cyanomethylcarboxamido-2-chloro-*β*-L-arabinose **3.**



1 **3**

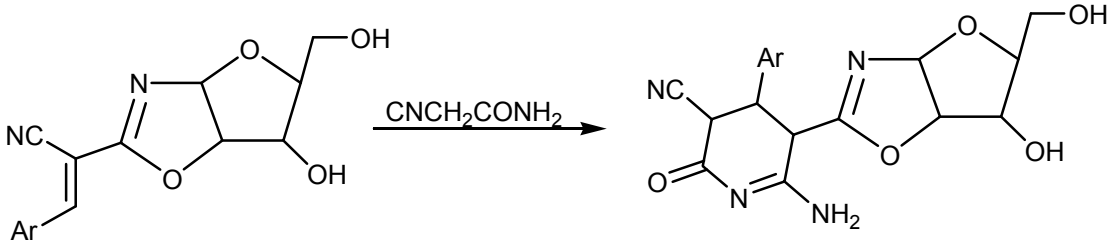
The structure of **3** was established on the basis of its elemental analysis and spectral data. For example, the ^{1}H NMR showed a resonance at approximately 9.1 ppm corresponding to the (NH)-function.

Subsequent, treatment of 2-cyanomethyl-*β*-L-arabinfurano[1`,2`:4,5] oxazoline **1** with benzaldehyde in the presence of triethylamine and ethanol under reflux for 3 hr, afforded 2-(2-phenyl-1-cyanoethenyl)-*β*-L-arabinofurano-[1`,2`:4,5]oxazoline **4**



1 **4**

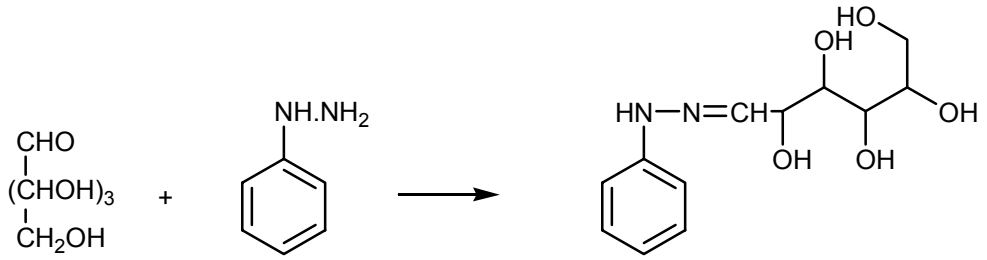
However, cyclization of compound **4** using cyanoacetamide in the presence of sodium ethoxide and ethanol afforded the cyclized compound **5**.



4 **5**

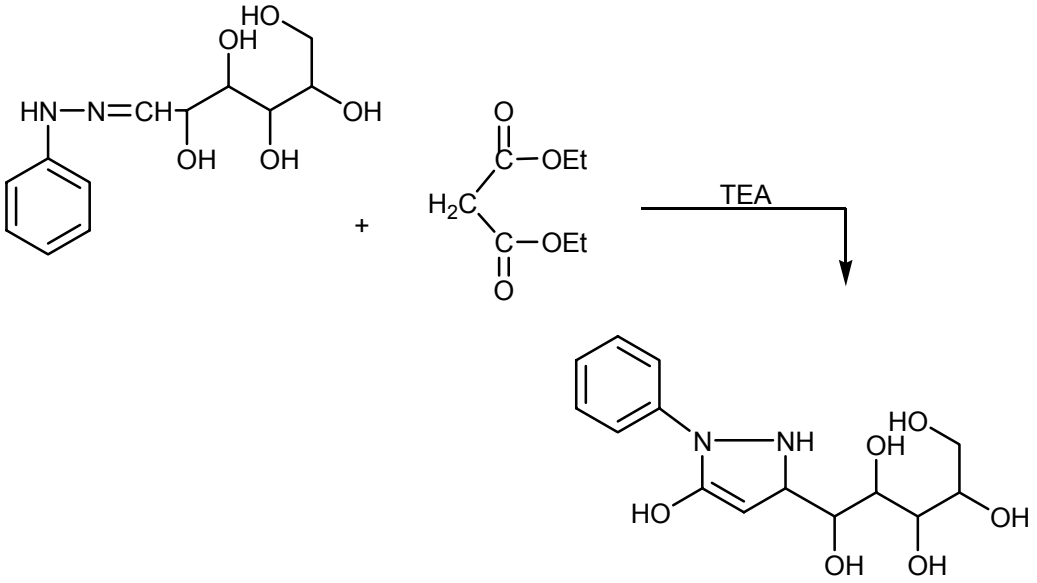
The structure of **5** was established on the basis of its elemental analysis and spectral data. The mass spectrum of **5** showed a molecular ion peak M^+ at (m/z: 370) supporting the molecular formula $C_{18}H_{18}N_4O_4$. It shows a fragmentation ion at m/e (353, 23.0%), (301, 42.1%) and (213, 45.6%).

In the present investigation, reaction of the D-glucose with phenylhydrazine in the presence of methanol under reflux was found to give the phenylhydrazone of glucose **6.**



6

Cyclization of **6** using diethylmalonate in the presence of triethylamine gave of 2, 5-dihydro-2-phenyl-5-(D-gluco-pentitolyl)-*1H*-pyrazol-3-ol **7**.



7

Antimicrobial activity

The activity of the synthesized products was tested by the disk diffusion method. The cup-plate technique was used for the determination of these antimicrobial effects. Antibacterial and antifungal assays using Whatman No. 4 filter paper discs (0.5 cm diameter) were soaked in the tested sample. The samples were dissolved in DMSO (dimethyl sulfoxide). 0.24 μg of each sample was dissolved in 0.1 ml DMSO**,** then 0.1 ml of each sample was used with some gram positive bacteria such as (*Sarcina lutea, Staphylococcus aureus* and *Bacillus subtilis*) , gram negative bacteria such as (*Pseudomonas aeuroginosa*, *Esherishia coli, Agrobacterium and Erwinia sp*.) and fungi (*Aspergillus niger, Penicillium funiculosum*) under aseptic conditions. The medium for cultivation of the test organisms was nutrient agar, and the Petri-dishes were incubated at 30 ^{o}C for 24 hrs. The results were obtained by measuring the inhibition zones (in

mm) caused by the various compounds on the microorganisms. From the results**,** it is obvious that most of the tested compounds posses slight or no activity at all towards the tested microorganisms. However**,** some compounds showed considerable activity against the tested bacteria such as **3, 4, 5**. Others exhibit moderate or slight activity against the fungi such as **6, 7.**

Table 1. Antimicrobial activity of the compounds considered

Compound	Zone of inhibition (mm) ** Microorganisms				
	1	2	3	4	5
1	15	-	15	-	-
2	15	13	-	-	-
3	23	-	14	-	-
4	-	20	15	-	-
5	-	14	14	14	-
6	15	15	-	-	-
7	-	-	-	-	-

* The solvent is dimethylsulfoxide (DMSO)

**1: Staphylococcus aureus

2: Pseudomonas aeuroginosa

3: Bacillus subtilis

4: Aspergillus niger

5: Penicillium funiculosum

The values are in mm diameter

Experimental Section

General Procedures. Melting points were determined with an Electro Thermal Mel-Temp II apparatus and are all uncorrected. IR spectra were obtained in the solid state as a potassium bromide disc using a Perkin-Elmer model 1430 Spectrometer. ^{1}H NMR were recorded on aVarian/Gemini 200/MHZ spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard (chemical shift in δ, ppm). Mass spectra were measured on an instrument "VG-7035". Spectra were recorded at 70 or 15 electron volt. Elemental analysis was performed at the Micro analytical centre, Cairo University, Giza, Egypt**.**

2-Cyanomethyl-β-L-arabinfurano [1`, 2`: 4, 5] oxazoline (1). A mixture of L-ararbinose (0.25 g, 1.65 mmole), malononitrile (0.48 g, 0.73 mmole), methanol (10 ml) and 6M NH_4OH (2 ml) was heated at 50^{o}C for 3 days. The reaction was cooled to 10^{o}C and kept at this

temperature overnight. The solvent was evaporated under reduced pressure and the residue recrystallized by methanol / diethyl ether to afford 67% yield as a brown crystals m.p. 120-124°C. IR (KBr) 3348 brs, 2188, 1650 cm^{-1} ; ^{1}H-NMR δ 5.65 (d, 1H, $H_{1`}$), 4.45 (s, 1H, OH-5), 4.75 (s, 1H, OH-3`), 2.5 (s, 2H, CH_2-CN), 3.5-3.7 (m, 5H, H-2,3,4,5,5`); M.S: M^+ ($C_8H_{10}N_2O_4$,198) Anal .calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.05; N, 14.14. Found: C, 48.37, H, 5.12; N, 14.22.

2-Methyl-4-oxothiazolyl-β-L-arabinfurano [1`,2`:4, 5] oxazoline (2). 2-Cyanomethyl-*β*-L-arabinfurano[1`,2`: 4,5]oxazoline **1** (0.3 g, 1.5 mmole), benzene (50 ml) and thioglycolic acid (2 ml) were refluxed 6 hrs. The solvent was evaporated, and the residue dissolved in chloroform the solution washed with $NaHCO_3$ solution. The organic layer was evaporated to yield 57% of compound **2** m.p. 195-198°C. IR (KBr) 1721 cm^{-1}; ^{1}H-NMR δ 6.13 (s, 1H, H_1), 5.98 (s, 1H, OH-5), 5.47 (s, 1H, OH-3), 4.21 (s, 2H, CH_2), 3.91-4.23 (m, 3H, H-2, 3, 4), 3.26 (s, 2H, CH_2-S). M.S: M^+ ($C_{10}H_{12}N_2O_5S$, 272.05) Anal. calcd. for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.41; N 10.29. Found. C, 44.26; H, 4.49; N,10.36.

1-Cyanomethylcarboxamido-2-chloro-β-L-arabinose (3). Acetyl chloride (5.2 ml) was added drop wise to a boiling suspension of **1** (0.24 g) in anhydrous acetonitrile (30 ml). The reaction mixture was stirred at 80°C for 4 hrs. After evaporation to dryness under reduced pressure, the residue was dissolved in dichloromethane (50 ml) and the solution was washed with water. The organic layer was separated and evaporated in vacuo to yield 51% of 1-cyanomethylcarboxamido-2-chloro-β-L-arabinose as brown crystals. m.p. 189-191 °C. IR (KBr) 3120, 1735, 2267 cm^{-1}. ^{1}H-NMR δ 9.1 (s, 1H, NH), 6.23 (d, 1H, H_1), 4.09 - 5.04 (m, 5H, H-2,3,4,5,5`), 3.50 (s, 2H, CH_2), 2.41 (2s, 6H, $2CH_3$). M.S: M^+($C_{12}H_{15}N_2O_6Cl$, 318.7) Anal. calcd. for $C_{12}H_{15}N_2O_6Cl$.: C, 45.18; H, 4.74; N, 11.12. Found. C, 45.26; H, 4.53; N, 11.32.

2-(2-Phenyl-1-cyano-ethenyl)-*β*-L-arabinofurano[1`,2`:4,5]oxazoline (4). A mixture of compound **1** (0.4 g, 2.02 mmole), benzaldehyde (0.3 g) and (0.1 ml) of triethylamine in absolute ethanol, and the mixture was refluxed for 3 hrs (progress the reaction was monitored by TLC), and the solvent was evaporated under reduce pressure. The residue was chromatographed on silica gel column (hexane-diethyl ether 2:1) to yield compound **4** (0.62 g) as yellow solid. m.p. 197-200°C. IR (KBr) 3394 brs, 2206, 1631, 1460 cm^{-1}. ^{1}H-NMR δ 7.13-7.30 (m, 5H, C_6H_5), 6.21 (d, 1H, C=CH), 5.47 (s, 2H, 2OH), 4.03-4.98 (m, 5H, H-2,3,4,5,5`) . M.S: M^+ ($C_{15}H_{14}N_2O_4$, 286.1): Anal. calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found C, 62.77; H, 4.81; N, 9.62.

2-[6-Amino-2,3,4,5-tetrahydro-2-oxo-4-phenylpyridine-3-carbonitrile]-*β*-L-arabinofurano[1`,2`:4,5]oxazoline (5). A mixture of compound **4** (0.3 g, 1.27 mmole), sodium ethoxide (0.02 g) and cyanoacetamide (0.1 g) in ethanol was heated under reflux for 6 hrs, then allowed to cool, poured into water, the solid product formed was filtrated off and recrystallized from ethanol to afford a pale yellow crystals (0.31 g), m.p. 237-240°C. IR (KBr)3438 brs, 2260, 1744, 1576 cm^{-1}; ^{1}H-NMR δ 7.43-7.49 (m, 5H, C_6H_5), 6.21 (s, 2H, NH_2), 5.26 (d, 1H, H_{-1}), 4.03-4.98 (m, 5H, H-2,3,4,5), 3.40 (d, 1H, CH-CN), 2.46 (d, 1H, Ar-H). M.S: M^+

($C_{18}H_{18}N_4O_5$, 370.13): Anal. calcd. for $C_{18}H_{18}N_4O_5$: C, 58.38; H, 4.86; N, 15.14. Found. C, 58.54; H, 4.93; N, 15.23.

***E*-6-[2-Phenylhydrazone)hexane-1,2,3,4,5-pentaol 6**

Glucosylphenylhydrazone (6). To a solution of D-glucose (1.80 g, 1 mmole) in methanol (5 ml) a warm solution of phenylhydrazine (1.53 g, 1 mmole) in methanol (70 ml), and concentrated hydrochloric acid (1 ml) was added. The reaction mixture was heated for 3 hrs at 70°C. After cooling the precipitated hydrazones was filtrated and recrystallized from aqueous methanol to give yellow crystals, yield 78%, m.p. 182-186°C. IR (KBr) 3461, 3304, 1602 cm^{-1}; ^1H NMR δ 9.04 (s, 1H, NH), 7.29-7.56 (m, 5H, C_6H_5), 6.82 (s, 1H, N=CH), 5.24 (s, 2H, OH-1, OH-2), 5.03 (s, 1H, OH-3), 3.89-3.55 (m, 5H, 2OH, H-2,3,4,5,5`). M.S: M^+ $C_{12}H_{18}N_2O_5$, 270.12,: Anal .calcd. for $C_{12}H_{18}N_2O_5$: C, 53.43; H, 6.71; N, 10.36. Found. C, 53.32; H, 6.52; N, 10.01.

2,5-Dihydro-2-phenyl-5-(D-gluco-pentitlo1yl)-*1H*-pyrazol-3-ol (7). A suspension of **6** (343 mg, 1 mmole) in methanol (50 ml) was added to diethyl malonate (2 g) in the presence of triethylamine (0.2 ml). The reaction mixture was refluxed for 4 hrs and then allowed to cool at room temperature. The precipitate was filtrated and washed with water (5ml), recrystallized from water to give orange crystals, yield 90%, m.p. 194-198°C. IR (KBr) 3324, 1603 cm^{-1}; ^1H NMR δ 12.13 (s, 1H, OH), 7.81 (s, 1H, NH), 5.82 (s, 1H, CH=C), 6.81-7.23 (m, 5H, C_6H_5), 6.79 (d, 1H, H-1`), 5.06 (s, 2H, OH-5, OH-1), 3.72 -4.47 ( m, 8H, 3OH, H-2,3,4, 5,5`). M.S: M^+ $C_{14}H_{20}N_2O_6$ 312.13 : Anal .calcd. for $C_{14}H_{20}N_2O_6$: C. 53.84; H, 6.42; N, 8.97. Found C, 52.41; H, 6.39; N, 8.88.

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