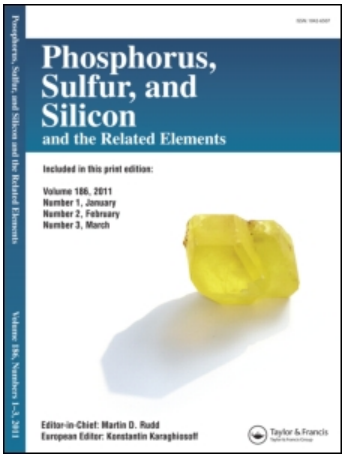


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Utilization of Dipotassium Salt of Galactaric Acid Bis(Hydrazidocarbodithioic Acid) As a Synthone for Double-Headed 1,3,4-Thiadiazoline, 1,3,4-Oxadiazoline and 1,2,4-Triazoline Acyclo C-Nucleosides

A. Z. Nasr[a]; M. A. Mostafa[b]
[a] Chemistry Department, Faculty of Science, Cairo University, Faiyoum, Egypt [b] Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

To cite this Article Nasr, A. Z. and Mostafa, M. A.(2005) 'Utilization of Dipotassium Salt of Galactaric Acid Bis(Hydrazidocarbodithioic Acid) As a Synthone for Double-Headed 1,3,4-Thiadiazoline, 1,3,4-Oxadiazoline and 1,2,4-Triazoline Acyclo C-Nucleosides', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 8, 1769 — 1779
To link to this Article: DOI: 10.1080/104265090888397
URL: http://dx.doi.org/10.1080/104265090888397

Phosphorus, Sulfur, and Silicon, 180:1769–1779, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090888397

Taylor & Francis
Taylor & Francis Group

Utilization of Dipotassium Salt of Galactaric Acid Bis(Hydrazidocarbodithioic Acid) As a Synthone for Double-Headed 1,3,4-Thiadiazoline, 1,3,4-Oxadiazoline and 1,2,4-Triazoline Acyclo C-Nucleosides

A. Z. Nasr
Chemistry Department, Faculty of Science, Cairo University, Faiyoum, Egypt

M. A. Mostafa
Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

*Condensation of galactaric acid bis hydrazide (**1**) with carbon disulfide in the presence of ethanolic potassium hydroxide gave the dipotassium salt of galactaric acid bis (hydrazidocarbodithioic acid) (**2**). Heterocyclization of the key compound **2** produced three different types of double headed acyclo* C*-nucleosides: acid-catalyzed dehydrative cyclization afforded the 5-thioxo-1,3,4-thiadiazoline **3**, base-catalyzed dehydrosulfurative cyclization gave the 5-thioxo-1,3,4-oxadiazoline **5**, and condensative cyclization with concomitant dehydrosulfuration and dehydration with different nitrogen nucleophiles yielded the 5-thioxo-1,2,4-triazolines **7** and **9a**, **b**. Acetylation of the prepared acyclo* C*-nucleosides **3**, **5**, **7** and **9a**, **b** with acetic anhydride in the presence of pyridine at ambient temperature caused acetylation of the sugar hydroxyls as well as heterocyclo imino protons to give the tetra*-O*-*acetates **4**, **6**, and **10a**, **b**, respectively. Representative members of the prepared compounds were tested for antimicrobial activity.*

Keywords 1,3,4-Oxadiazoline; 1,3,4-thiadiazoline; 1,2,4-triazoline; acyclo *C*-nucleosides; antimicrobial activity; cyclization; dipotassium salt of galactaric acid bis(hydrazidocarbodithioic acid)

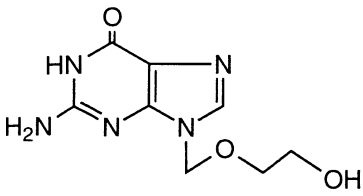
INTRODUCTION

Much of the interest in the synthesis[1–7] of acyclo *C*-nucleosides originated from their various biological activities as a result of their close

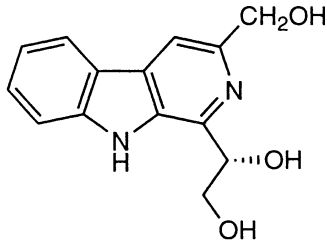
Received May 3, 2004; accepted July 28, 2004.

Our thanks are due to Dr. Hanan Ghozlan, Department of Botany and Microbiolgy, Faculty of Science, Alexandria University for performing the antimicrobial activities.

Address correspondence to A. Z. Nasr, Chemistry Department, Faculty of Science, Cairo University, Faiyoum 63514, Egypt. E-mail: adelznasr@hotmail.com



acyclovir



pyridindolol

FIGURE 1

structural relationship with acyclo *N*-nucleosides, such as the potent antiviral agent "acyclovir" [9-(2-hydroxyethoxymethyl)guanine].[8,9] Furthermore, acyclo *C*-nucleosides has become an increasingly important class of compounds, especially after the isolation of the naturally occuring acyclo *C*-nucleoside members such as pyridindolol[10,11] and the two antibiotics CV-1[12] and gualamycin[13–15] from different species of *Streptomyces*. Many 1,2,4-triazole *C*-nucleosides[16–18] as well as their acyclo analogs[19–23] have been synthesized in view of their ability to mimic the isosteric broad spectrum antiviral 1,2,4-triazole ribonucleoside "ribavirin" (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide).[24] On the other hand, synthesis of thioxo derivatives of 1,3,4-thiadiazolines, 1,3,4-oxadiazolines, and 1,2,4-triazolines is of interest since many of their members possess various biological activities. These activities include antimicrobial[25] and antitubercular[26,27] for 1,3,4-thiadiazolines, antibacterial[28,29] and antiiflammatory[30] for 1,3,4-oxadiazolines, and antidepressant,[31] antiviral,[32] antiinflammatary,[33] and analgesic[34] for 1,2,4-triazolines. In pursuance of our work on the synthesis of acyclo *C*-nucleosides of potential activity,[35–38] we presently report on the utilization of dipotassium salt of galactaric acid bis(hydrazidocarbodithioic acid) as a synthone for double-headed 5-thioxo-1,3,4-thiadiazoline, 5-thioxo-1,3,4-oxadiazoline and 5-thioxo-1,2,4-triazoline acyclo *C*-nucleosides by choosing the proper heterocyclizing agent (Figure 1).

DISCUSSION

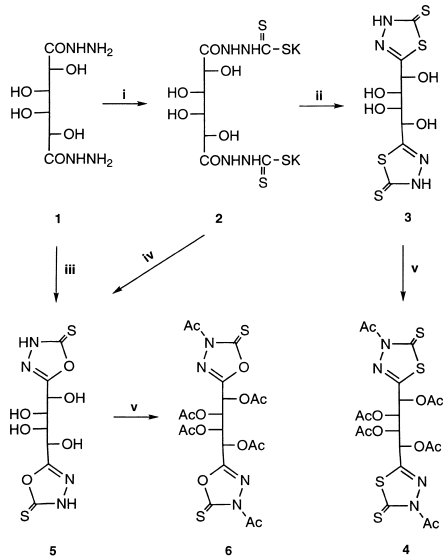
Condensation of galactaric acid bis hydrazide[39] (**1**) with carbon disulfide in the presence of an ethanolic potassium hydroxide at ambient temperature gave the dipotossium salt of galactaric acid bis (hydrazidocarbodithioic acid) (**2**). The latter compound underwent acid-catalyzed

dehydrocyclization with sulfuric acid in methanol at room temperature to give a crystalline product. This product showed IR absorption at 3278 (overlapped OH and NH), 1645 (C = N), and 1236 cm^{-1} (CNS), and its ^1H NMR spectrum displayed signals of two imino protons in addition to four OH and four CH protons of the tetritolyl moiety. It analyzed for the molecular formula $C_8H_{10}N_4O_4S_4$ and is, accordingly, assigned the structure of 1,4-bis(5-thioxo-1,3,4-thiadiazolin-2-yl)-*galacto*-tetritol (**3**). This result is in accordance with the precedent and already-established results[40,41] on acid catalyzed dehydrocyclization of similar hydrazidocarbodithioates. The mass spectrum of (**3**) did not reveal its molecular ion peak, yet it showed fragments that are characteristic of the assigned structure at *m/z* 196 resulting from C1-C2 bond clevage of the tetritolyl moiety and another fragment at *m/z* 147 corresponding to 5-thioxo-1,3,4-thiadiazoline ring carring a protonated formyl group. The latter fragment is characteristic of *C*-nucleosides as well as their acyclo analogs.[42]

On the other hand, base-catalyzed dehydrosulfurative cyclization of compound **2** by heating with ethanolic potassium hydroxide gave a product that analyzed correctly for $C_8H_{10}N_4O_6S_2$ and was ascribed, therefore, the 1,4-bis(5-thioxo-1,3,4-oxadiazolin-2-yl)-*galacto*-tetritol structure (**5**). This structure **5** was evidenced by its IR absorptions at 3329 (overlapped OH and NH), 1591 (C=N) and 1285 cm^{-1} (NCS), as well as its ^1H NMR spectrum which revealed proton signals due to the oxadiazolinyl two NH in addition to the tetritolyl four OH and four CH protons. An additional one-step cyclocondensation was used for the synthesis of compound **5** by heating the bis hydrazide **1** with carbon disulfide in ethanolic potassium hydroxide. This result is in harmony with previous work[28,43,44] on the synthesis of thioxo-1,3,4-oxadiazolines from aroylhydrazines by the same method.

The two acyclo *C*-nuleosides **3** and **5** were further characterized by acetylation with acetic anhydride in the presence of pyridine at ambient temperature to give the 1,2,3,4-tetra-*O*-acetyl-1,4-bis(4-acetyl-5- thioxo-1,3,4-thiadiazolin-2-yl)-*galacto*-tetritol (**4**) and its 1,3,4-oxadiazolin-2-yl congener **6**, respectively. Both compounds exhibited ^1H NMR proton signals of the tetra-*O*-acetyl-tetritolyl chain (4 CH and 4 $OCOH_3$) and the two *N*-acetyl groups. They also showed IR absorption due to OAc, CON, C=N, and NCS groups. The mass spectrum of compound **6** showed its molecular ion peak M^+ at *m/z* 574 in addition to characteristic fragments at *m/z* 514 (M^+–AcOH), *m/z* 490 (M^+–2 CH_2CO), and *m/z* 287 (C1-C2 fission of the sugar chain) (Scheme 1).

Condensative cyclization with concomitant dehydrosulfuration and dehydration of the dithioic salt **2** has been accomplished by heating



(i) CS_2, KOH-EtOH, RT, 24h; (ii) 0.1M H_2SO_4–MeOH, RT, 2h;
(iii) CS_2, KOH-EtOH, reflux, 6h; (iv) KOH-EtOH, reflux, 4h;
(v) Ac_2O, pyridine, RT, 72h .

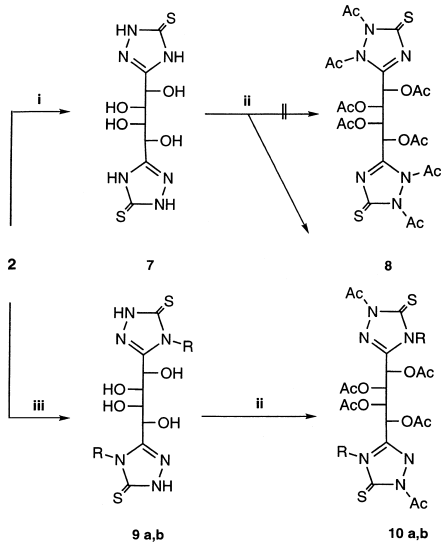
SCHEME 1

with ammonium acetate to give the 1,4-bis(5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetrilol (**7**). The latter structure **7** was assigned on the basis of its IR absorptions at 3328 (overlapped OH and NH), 1642 (C=N), and 1284 cm^{-1} (NCS) as well as its ^1H NMR spectrum which displayed proton signals due to eight exchangeable protons: four NH protons resonated as two singlet signals at δ 13.12, and 12.99, and tetritolyl four OH protons appeared as two doublet signals at 5.85 and 5.19, in addition to the tetritolyl four CH protons as two doublet signals at δ 4.41 and 4.22 ppm.

Subjecting compound **7** to acetylation gave a single crystalline product lacking the OH and NH IR absorptions as well as ^1H NMR triazolinyl four NH and tetritolyl four OH proton signals and analyzed for $C_{24}H_{28}N_6O_{12}S_2$, indicating the introduction of eight acetyl groups in the parent molecule, four of which as *O*-acetyl groups blocking the tetritolyl chain hydroxyl protons and the other four migh has acetylated the triazolinyl N1 and N2 or N1 and N4 of each of the two triazoline rings. These data are consistent with either of the structure **8** or **10a**. The acetylation product was assigned the 1,4-di-*N*-acetyl structure **10a** rather than the 1,2-di-*N*-acetyl structure **8** on the basis of direct comparison

with the unequivocally prepared sample from acetylation of 1,4-bis(4-acetyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacte*-tetritol (**9a**) prepared from cyclization of the compound **2** with acetamide. This assignment is in agreement with the reported result[45] documenting the preference of acetylation of triazolinyl N1 and N4 rather than N1 and N2.

Similarly, heterocyclization of the dithioate **2** by heating with methylamine afforded the 1,4-bis(4-methyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol **9b**). It's ^{1}H NMR spectrum showed, beside the tetritolyl chain protons (4 OH and 4CH), two imino protons and two *N*-methyl group protons. Acetylation of the triazoline **9b** caused *N*-acetylation of the two triazoline moieties as well as *O*-acetylation of the tetritolyl chain four OH groups to give the 1,2,3,4-tetra-*O*-acetyl-1,4-bis(1-acetyl-4-methyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (**10b**), which revealed IR absorptions characteristic of OAc, CON, C═N, and NCS groups and lacked the OH and NH absorptions of the parent compound **9b**. The structure of tetra-*O*-acetate compound **10b** was also supported by its ^{1}H NMR spectrum, which revealed the tetra-*O*-acetyl-tetritolyl chain protons (4 CH and 4 OAc) in addition to the two triazolinyl *N*-acetyl and *N*-methyl groups (Scheme 2).



(i) $AcONH_4$, reflux, 1.5h; (ii) Ac_2O, pyridine, RT, 72h;
(iii) RNH_2, a, R = Ac, reflux, 1.5h; b, R = Me, reflux, 6h

SCHEME 2

TABLE I Antibacterial and Antifungal Activities of Selected Compounds

Compound	Conc. (mg/mL)	Inhibition Zones* (mm) *E. coli*	*S. aureus*	*C. albicans*
3	0.3	25	0	20
4	0.3	13	0	13
5	0.3	14	15	15
7	0.3	14	0	15
10a	0.3	18	0	15
Ampicillin	0.3	21	17	—
Cansten	0.3	—	—	33
DMF	Solvent	6.5	0	—

*Inhibition zones of less than 10 mm in diameter were considered to indicate weak activity.

Compounds **3**, **4**, **5**, **7**, and **10a** were screened for their antibacterial activity *in vitro* against the Gram-negative bacterium *Escherichia coli* and the Gram-positive bacterium *Staphylococcus aureus* as well as for antifungal activity against *Candida albicans* using the agar diffusion method.[46] Compound **3** showed fair activity against *E. coli* and *C. albicans* and lacked activity against *S. aureus*, while compound **5** showed activity only against *S. aureus* (see Table I).

EXPERIMENTAL

Melting points were determined on MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The infrared spectra IR were recorded for potassium bromide discs on a Pye-Unicam SP1025 spectrophotometer. Proton magnetic resonance ^{1}H NMR spectra were carried out at ambient temperature (~25°C) with a Varian EM-390 or with a Brucker AC-250 spectrometer using Tetramethylsilane (TMS) as an internal standard. Mass Spectra (MS) were preformed on a Hewlett Packard 5995 gas chromatography mass-spectrometer system. Homogeneity of the products and follow up of the reactions were checked by ascending thin-layer chromatography TLC on plates precoated with silica gel G (E. Merck; layer thickness 0.25 mm) used without pretreatment. All ratios of the used solvent systems were volume to volume V/V, the solvent system used were (a) $CHCl_3$/MeOH (1:2) and (b) $CHCl_3$/MeOH (9:1); the distance of the solvent travel was 5 cm and the spots were visualized by exposure to iodine vapor for a few minutes. Elemental microanalysis was performed at the Microanalytical Unit, Cairo University, Cairo, Egypt.

1,4-Bis(5-thioxo-1,3,4-thiadiazol-2-yl)-*galacto*-tetritol (3)

A stirred suspension of galactaric acid bis hydrazide (**1**) (3 g, 12.6 mmol) in absolute ethanol (50 mL) was treated with a solution of potassium hydroxide (1.7 g, 30.4 mmol) in absolute ethanol (50 mL) follwed by carbon disulfide (3 mL) and the reaction mixture was stirred at ambient temperature for 24 h. The product was filtered and washed with ether to give the dipotassium salt of galactaric acid bis (hydrazidocarbodithioic acid) (**2**) (yield: 4.7 g, 80%). A suspension of the **2** (4 g, 8.6 mmol) in methanol (50 mL) was treated with 0.1 M sulfuric acid (7 mL) in methanol (50 mL) and the mixture was stirred at room temperature for 2 h. The product was filtered, washed with ethanol, and then crystallized from water-ethanol (1:1) to give compound **3** as colorless crystals (yield: 2.5 g, 82%). mp: 198–200°C. TLC (A), R_f: 0.51. IR ν_{max} (KBr) cm^{-1}: 3278 (broad, overlapped OH and NH), 1645 (C=N), 1236 (NC=S). ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.76, 4.18 (2 d, 2 H each, tetritoldi-1,4-yl), 4.40, 5.15 (2d, exchangeable, 2 OH each), 12.79 (s, exchangeable, 2 NH). MS *m/z* (rel. int.): 196 (2.5), 147 (50), 118 (100). Anal. Calcd. for $C_8H_{10}N_4O_4S_4$: C, 27.12; H, 2.82; N, 15.82. Found: C, 26.98; H, 2.71; N, 15.53.

1,4-Bis(5-thioxo-1,3,4-oxadiazolin-2-yl)-*galacto*-tetritol (5)

Method 1

Dipotassium salt **2** (4 g, 8.6 mmol) was treated with a solution of 0.2 M ethanolic potassium hydroxide (100 mL) and the mixture was refluxed for 4 h. After attaining room temperature, the reaction mixture was neutralized with 0.1 M hydrochloric acid and the product was filtered, washed with ethanol, and crystallized from water-ethanol (1:1) to give compound **5** as colorless crystals (yield: 2.5 g, 82%). mp: 186–188°C. TLC (A), R_f: 0.52. IR ν_{max} (KBr) cm^{-1}: 3329 (broad, overlapped OH and NH), 1591 (C=N), 1285 (NC=S). ^1H NMR (DMSO-d_6, 300MHz) δ: 4.05, 4.56 (2 d, 2 H each, tetritoldi-1,4-yl), 5.53, 5.68 (2 d, exchangeable, 2 OH each), 13.19 (s, exchangeable, 2 NH). Anal. Calcd. for $C_8H_{10}N_4O_6S_2$: C, 29.81; H, 3.11; N, 17.39. Found: C, 29.57; H, 2.98; N, 17.75.

Method 2

Bis hydrazide **1** (3 g, 8.4 mmol) was treated with a solution of potassium hydroxide (1.9 g, 33.9 mmol) in absolute ethanol (100 mL) followed by carbon disulfide (3 mL) and the reaction mixture was refluxed for 6 h. After attaining room temperature, the reaction mixture was neutralized with 0.1 M hydrochloric acid and the product was filtered, washed with ethanol, and crystallized from water-ethanol (1:1) to give

compound **5** (yield: 2.1 g, 78%). mp, TLC, and IR are identical to those of compound **5** when prepared according to method 1.

1,4-Bis(5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (7)

Dipotassium salt **2** (4 g, 8.6 mmol) was successively mixed with anhydrous ammonium acetate (1.4 g, 18.2 mmol) and the mixture was heated in a fusion tube provided with an air condenser at 100°C for 1 h. Heating was continued in an oil bath at 140°C for additional 0.5 h. The obtained mass was dissolved in water-ethanol (1:3) (50 mL), treated with 0.1 M hydrochloric acid (15 mL), and the product was filtered and crystallized from water-ethanol (1:1) to give compound **7** as colorless crystals (yield: 2g, 71%). mp: 220–222°C. TLC (A), R_f: 0.50. IR ν_{max} (KBr) cm^{-1}: 3328 (broad, overlapped OH and NH), 1642 (C=N), 1284 (NC=S). ^1H NMR (DMSO-d_6, 300MHz) δ: 4.22, 4.41 (2 d, 2 H each, tetritoldi-1,4-yl), 5.19, 5.85 (2 d, exchangeable, 2 OH each), 12.99, 13.12 (2 s, exchangeable, 2 NH each). Anal. Calcd. for $C_8H_{12}N_6O_4S_2$: C, 30.00; H, 3.75; N, 26.25. Found: C, 30.30; H, 3.59; N, 26.41.

1,4-Bis(4-acetyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (9a)

The title compound was prepared from dipotassium salt **2** (4 g, 8.6 mmol) and acetamide (1.1 g, 18.6 mmol) as just described for the prepareation of compound **7**. It crystallized from water-ethanol (1:1) to give compound **9a** as colorless crystals (yield: 2.6 g, 74%). mp: 168–170°C. TLC (A), R_f: 0.48. IR ν_{max} (KBr) cm^{-1}: 3377 (broad, overlapped OH and NH), 1683 (NC=O), 1604 (C=N), 1274 (NC=S). ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.08 (s, 6 H, 2 NAc) 3.78, 4.60 (2 d, 2 H each, tetritoldi-1,4-yl), 5.14, 6.67 (2 bs, exchangeable, 2 OH each), 12.80 (bs, exchangeable, 2 NH). Anal. Calcd. for $C_{12}H_{16}N_6O_6S_2$: C, 35.64; H, 3.96; N, 20.79. Found: C, 35.91; H, 3.76; N, 20.59.

1,4-Bis(4-methyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (9b)

Dipotassium salt **2** (4 g, 8.6 mmol) was treated with methylamine (50 mL) and the mixture was refluxed for 6 h. The mixture was evaporated to dryness and the residue obtained was dissolved in water-ethanol (1:3) (50 mL), treated with 0.1 M hydrochloric acid (15 mL), and was filtered and crystallized from water-ethanol (1:1) to compound **9b** as colorless crystals (yield: 2.3 g, 77%). mp: 260-262°C. TLC (B), R_f: 0.57. IR ν_{max} (KBr) cm^{-1}: 3296 (broad, overlapped OH, NH), 1650 (C=N), 1271 (NC=S). ^1H NMR (DMSO-d_6, 300MHz) δ: 3.73 (s, 6 H, 2 NMe), 4.08,

4.53 (2 d, 2 H each, tetritoldi-1,4-yl), 5.47, 6.07 (2 d, exchangeable, 2 OH each), 12.83 (bs, exchangeable, 2 NH). Anal. Calcd. for $C_{10}H_{16}N_6O_4S_2$: C, 34.48; H, 4.60; N, 24.14. Found: C, 34.29; H, 4.81; N, 24.39.

Acetylation of the Acyclo *C*-Nucleosides 3, 5, 7, and 9a,b

A mixture of the appropriate compound **3**, **a**, **7**, or **9a**, **b** (2 g, 5–6.2 mmol), pyridine (10 mL) and acetic anhydride (50 mL) was stirred at room temperature for 72 h. The mixture was poured onto crushed ice and the product was filtered, washed with water, dried, and crystallized from ethanol. The following compounds were prepared.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis(4-acetyl-5-thioxo-1,3,4-thiadiazolin-2-yl)-*galacto*-tetritol (4)

Colorless crystals yield, (2.6 g, 77%). mp: 253–255°C. TLC (B), R_f: 0.56. IR ν_{max} (KBr) cm^{-1}: 1758 (OAc), 1684 (NC=O), 1607 (C=N). ^1H NMR ($CDCl_3$, 300MHz) δ: 2.11, 2.17 (2 s, 6 H each, 4 OAc), 2.64 (s, 6 H, 2 NAc), 5.69, 6.42 (2 s, 2 H each, tetritoldi-1,4-yl). Anal. Calcd. for $C_{20}H_{22}N_4O_{10}S_4$: C, 39.60; H, 3.63; N, 9.24. Found: C, 39.37; H, 3.42; N, 9.44.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis(4-acetyl-5-thioxo-1,3,4-oxadiazolin-2-yl)-*galacto*-tetritol (6)

Colorless crystals yield, (2.9 g, 81%). mp: 203–204°C. TLC (B), R_f: 0.51. IR ν_{max} (KBr) cm^{-1}: 1761 (OAc), 1693 (NC=O), 1590 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.11, 2.14 (2 s, 6 H each, 4 OAc), 3.05 (s, 6 H, 2 NAc), 5.59, 6.53 (2 s, 2 H ech, tetritoldi-1,4-yl). MS *m/z* (rel. int.): 574 (7.1) M^+, 514 (4.8), 490 (15.5), 287 (8.1), 172 (100). Anal. Calcd. for $C_{20}H_{22}N_4O_{12}S_2$: C, 41.81; H, 3.83; N, 9.76. Found: C, 42.01; H, 3.69; N, 9.93.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis(1,4-diacetyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (10a)

Colorless crystals yield, (method 1: 3.1 g, 76%; method 2: 2.4 g, 73%). mp: 265–267°C. TLC (B), R_f: 0.61. IR ν_{max} (KBr) cm^{-1}: 1758 (OAc), 1695 (NC=O), 1590 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.10, 2.16 (2 s, 6 H each, 4 OAc), 2.86, 3.16 (2 s, 6 H each, 4 NAc), 5.57, 6.52 (2 s, 2 H each, tetritoldi-1,4-yl). Anal. Calc. for $C_{24}H_{28}N_6O_{12}S_2$: C, 43.90; H, 4.27; N, 12.81. Found: C, 44.17; 4, 4.01; N, 13.02.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis(1-acetyl-4-methyl-5-thioxo-1,2,4-triazolin-3-yl)-*galacto*-tetritol (10b)

Colorless crystals yield, (2.2 g, 71%). mp: 277–279°C. TLC (B), R_f: 0.63. IR ν_{max} (KBr) cm^{-1}: 1743 (OAc), 1678 (NC=O), 1629 (C=N). ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.13, 2.19 (2 s, 6 H each, 4 OAc), 2.87, 3.53 (2 s, 6 H each, 2 NAc, 2 NMe), 5.56, 6.52 (2 s, 2 H each, tetritoldi-1,4-yl). Anal. Calcd. for $C_{22}H_{28}N_6O_{10}S_2$: C, 44.00; H, 4.67; N, 14.00. Found: C, 44.23; H, 4.49; N, 14.31.

Antimicrobial Activity

Sterile nutrient agar (100 mL) was separately inoculated with a 24-hour broth culture (1 mL) of *E. coli*, *S. aureus*, and *C. albicans*. Solutions (30 μL) of the tested compounds were placed in wells (6 mm diam.) cut in the agar media and the plates were incubated at 37°C (bacteria) or 25°C (yeast). The diameter of the resulting inhibition zones obtained were measured after 28 h for bacteria and 96 h for the yeast (see Table 1).

REFERENCES

[1] R. J. Remy and J. A. Secrist III, *Nucleoside Nucleotides*, **4,** 411 (1985).
[2] C. K. Chu and S. J. Cutlar, *J. Heterocycl. Chem.*, **23,** 289 (1986).
[3] M. A. E. Shaban and A. Z. Nasr, *Adv. Heterocycl. Chem.*, **68,** 223 (1997).
[4] M. A. E. Shaban, *Adv. Heterocycl. Chem.*, **70,** 163 (1998).
[5] E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem.*, **67,** 391 (1997).
[6] E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem.*, **68,** 1 (1997).
[7] E. S. H. El Ashry and Y. El Kilany, *Adv. Heterocycl. Chem.*, **69,** 129 (1998).
[8] G. B. Elion, P. A. Furman, J. A. Fyfe, P. De Miranda, L. Beauchamp, and H. Schaeffer, *J. Proc. Nat. Acad. Sci. USA*, **74,** 5716 (1977).
[9] H. J. Schaeffer, L. Beauchamp, P. De Miranda, G. Elion, D. J. Bauer, and P. Collins, *Nature (London)* **212,** 583 (1987).
[10] T. Aoyagi, M. Kumagai, T. Hazato, H. Hamada, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, **28,** 555 (1975).
[11] M. Kumagai, H. Naganawa, T. Aoyagi, H. Umezaw, H. Nakamura, and Y. Iitaka, *J. Antibiot.*, **28,** 876 (1975).
[12] T. Yasuzawa, M. Yoshida, M. Ichimura, K. Shirahata, and H. Sano, *J. Antibiot.*, **40,** 727 (1987).
[13] K. Tsuchiya, S. Kobayashi, T. Harada, T. Kurakawa, T. Nakagawa, and N. Shimada, *J. Antibiot.*, **48,** 626 (1995).
[14] K. Tsuchiya, S. Kobayashi, T. Kurokawa, T. Nakagawa, N. Shimada, H. Nakamura, et al. *J. Antibiot.*, **48,** 630 (1995).
[15] K. Tatsuta, M. Kitagawa, T. Toriuchi, K. Tsuchiya, and N. Shimada, *J. Antibiot.*, **48,** 741 (1995).
[16] M. S. Poonian and E. F. Nowoswiat, *J. Org. Chem.*, **45,** 203 (1980).
[17] N. Katagiri, N. Tabei, S. Atsuumi, T. Haneda, and T. Kato, *Chem. Pharm. Bull.*, **33,** 102 (1985).

[18] G. Y.Shen, R. K. Robins, and G. R. Revankar, *Nucleosides Nucleotides & Nucleic Acids*, **10,** 1707 (1991).
[19] H. Kristen, I. Meerwald, and A. Börner, *Pharmazie* **41,** 551 (1986).
[20] H. Kristen and I. Meerwald, Ger. (East) DD 245875 (1987); *Chem. Abstr.*, **107,** 237221 (1987).
[21] M. A. E.Shaban, A. Z. Nasr, and M. A. M. Taha, *J. Carbohydr. Chem.*, **14,** 985 (1995).
[22] A. Z. Nasr, *Alex. J. Pharm. Sci.*, **10,** 139 (1996); *Chem. Abstr.*, **125,** 301457 (1996).
[23] E. S. H. El Ashry and L. F. Awad, *Nucleosides Nucleotides & Nucleic Acids*, **20,** 901 (2001).
[24] B. E. Gilbert and V. Knight, *Antimicrob. Agents Chemother.*, **30,** 201 (1986).
[25] M. A. E. Shaban, M. F. Iskander, and S. M. El-Badry, *Pharmazie*, **52,** 350 (1997).
[26] M. Kidwai, R. Kumar, A. Srivastava, and H. P. Gupta, *Bioorg. Chem.*, **26,** 289 (1998).
[27] A. Foroumadi, Z. Kiani, and F. Soltani, *Il Farmaco*, **58,** 1073 (2003).
[28] T. P. Dabhi, V. H. Shah, and A. R. Parikh, *Indian J. Pharm. Sci.*, **54,** 98 (1992).
[29] M. Mashaly, M. N. Khodeir, M. Hanna, and H. El-Shafei, *Boll Chim. Farm.*, **134,** 28 (1995); *Chem. Abstr.*, **124,** 117178 (1996).
[30] U. V. Laddi, S. R. Desai, and S. C. Bennur, *Indian Drugs*, **34,** 666 (1997).
[31] J. M. Kane, M. W. Dudley, S. M. Sorensen, and F. P. Miller, *J. Med. Chem.*, **31,** 1253 (1988).
[32] B. Gabrielsen, M. J. Phelan, L. Barthel-Rose, C. See, J. W. Huggins, D. F. Kafauver, et al. *J. Med. Chem.*, **35,** 3231 (1992).
[33] E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu, and G. Altinak, *Il Farmaco*, **57,** 101 (2002).
[34] G. Turan-Zitouni, Z. A. Kaplanciki, K. Erol, and F. S. Kiliç, *Il Farmaco*, **54,** 218 (1999).
[35] A. Z. Nasr, *Nucleosides, Nucleotides & Nucleic Acids*, **22,** 349 (2003).
[36] M. A. E. Shaban, A. Z. Nasr, and A. E. A. Morgaan, *Pharmazie*, **54,** 580 (1999).
[37] M. A. E. Shaban, M. A. Mostafa, and A. Z. Nasr, *Pharmazie*, **58,** 367 (2003).
[38] M. A. E. Shaban, A. Z. Nasr, and A. E. A. Morgaan, *Pharmazie*, **58,** 860 (2003).
[39] T. Curtius and A. Darapsky, *J. Prakt. Chem.*, **95,** 168 (1917).
[40] E. M. E. Mansour, A. A. Kassem, T. M. Abass, A. A. El-Toukhy, and M. A. M. Nassr, *J. Prakt, Chem.*, **333,** 339 (1991).
[41] E. M. E. Mansour, A. A. Kassem, T. M. Abass, A. A. El-Toukhy, and M. A. M. Nassr, *J. Carbohydr. Chem.*, **10,** 429 (1991).
[42] L. B. Townsend and R. K. Robins, *J. Heterocycl. Chem.*, **6,** 459 (1969).
[43] S. E. Abbas, A. E. Abou-Youssef, G. M. El-Taliawi and A. B. Hassan, *Egypt. J. Pharm. Sci.*, **32,** 515 (1991); *Chem. Abstr.*, **118,** 101881 (1993).
[44] R. N. Vansdadia and H. Parekh, *J. Inst. Chem.* **64,** 49 (1992); *Chem. Abstr.*, **119,** 8745 (1993).
[45] E. B. Usova, G. D. Krapivin, V. E. Zavodnik and V. G. Kulnevich, *Khim. Geterotsikl. Soedin.*, **30,** 1337 (1994); *Chem. Abstr.*, **123,** 83281 (1995).
[46] T. Yousef and G. G. Tawil, *Pharmazie*, **35,** 698 (1980).