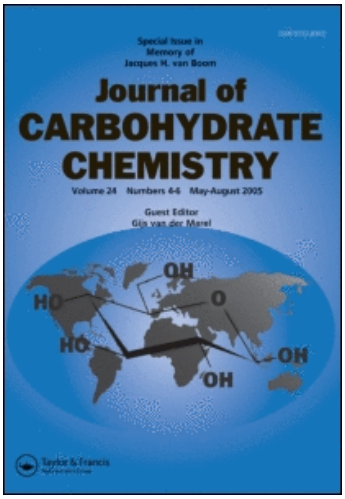

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SELECTIVE CYCLISATION OF 2,3,4,5-TETRA-O-ACETYLGALACTARIC ACID BIS[ALKYLTHIO(THIOCARBONYL)]HYDRAZIDES TO SACCHARIDE 1,3,4-OXADIAZOLE, THIADIAZOLE, AND THIADIAZOLINE DERIVATIVES

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ABSTRACT

The syntheses of galactaric acid acetate bis[alkylthio-(thiocarbonyl)]hydrazides (1,2) are described. Selective cyclisation of both hydrazide 1 and 2 was investigated. Using phosphorous oxychloride as a cyclising agent, loss of water produced 1,2,3,4-tetra-O-acetyl-1,4-bis(5-S-methyl or benzyl)-1,3,4-thiadiazol-2-yl)galacto-tetritol (3) or (4). Use of thionyl chloride lead to dehydrosulfurization and gave 1,2,3,4-tetra-O-acetyl-1,4-bis(5-S-methyl or benzyl)-1,3,4-oxadiazol-2-yl)galacto-tetritol (5) or (6). Finally, with triethyl orthoformate as the cyclising agent, compound 1 or 2 gave 3,3'-(2,3,4,5-tetra-O-acetylgalactar-1,6-dioyl)-bis-[(2-ethoxy-2,3-dihydro-5-S-methyl or benzyl)-1,3,4-thiadiazole] (7) or (8).

INTRODUCTION

Saccharide-hydrazides are of importance, as a source of saccharide-1,3,4-oxadiazole,[1-3] 1,3,4-thiadiazole,[4] and 1,3,4-oxadiazoline derivatives.[5,6] These heterocyclic compounds are of biological and industrial interest and have found uses as fungicidal[7,8] and bactericidal[9] agents, with some having analgetic antipyretic, paralytic and/or sedative

properties.[10-12] They are also used as carcinogenic,[13] anti-convulsive,[14] and muscle-relaxation agents.[15] In addition to their biologically interesting properties, they have properties as light scattering agents and as scintillators,[16] and as insecticides.[17]

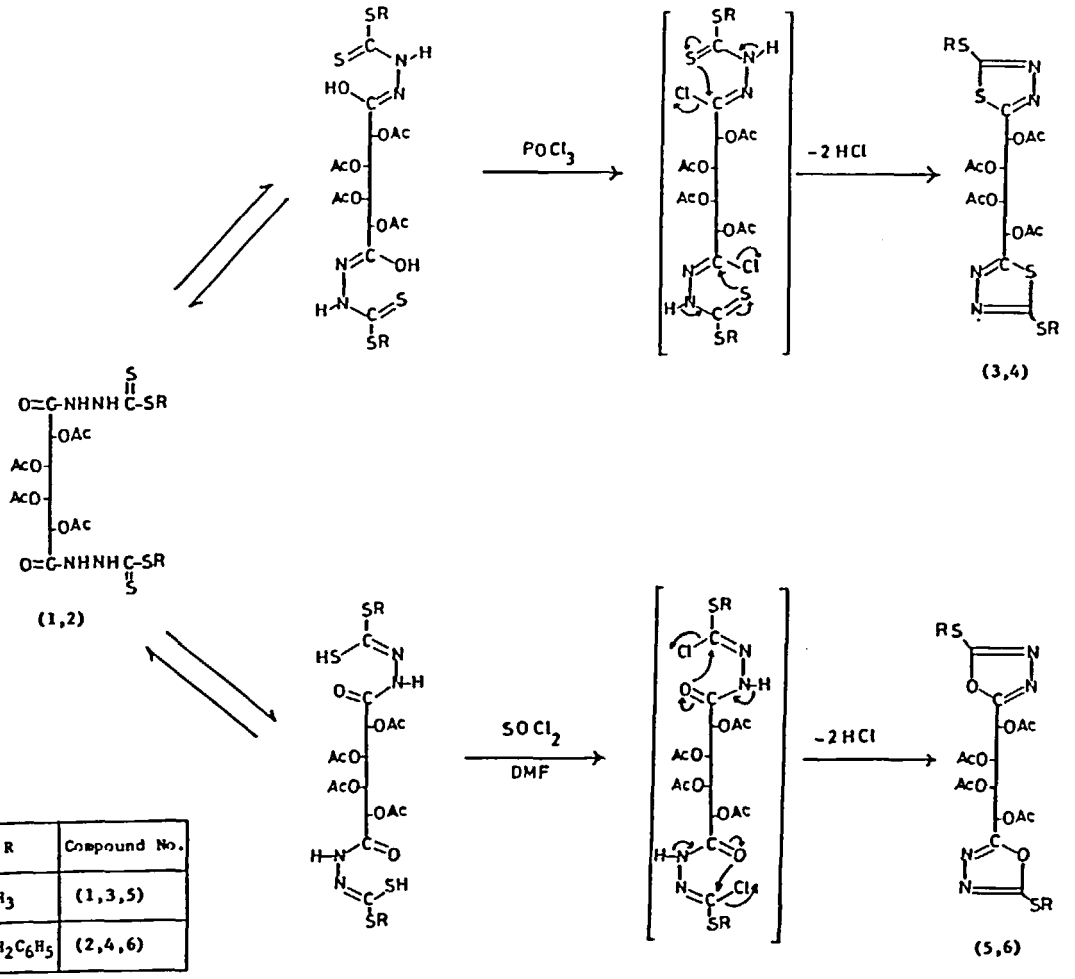
Dehydrative, and condensative cyclisation were reported for aldaric acid bis(aroylhydrazide) acetates, when heated with thionyl chloride, phosphorous oxychloride, or triethyl orthoformate.[1-6,18] In the present work, we tried to use the selectivity of these different cyclising agents on saccharide-bis(hydrazides) containing sulfur to produce different types of saccharide-bis(heterocyclic) compounds containing sulfur.

RESULTS AND DISCUSSION

This work is concerned with the cyclisation of new saccharide-bis(hydrazides) containing sulfur. The type of saccharide-bis(heterocyclic) products formed are dependent on the type of cyclising agents employed. With thionyl chloride, the corresponding 1,3,4-oxadiazole derivatives were formed with elimination of hydrogen sulfide. Employing phosphorous oxychloride as the reagent produced the corresponding 1,3,4-thiadiazole derivatives, with water elimination, whereas using triethyl orthdformate gave the corresponding 1,3,4-thiadiazoline derivatives.

The condensation of 2,3,4,5-tetra-O-acetyl galactaroyl dichloride[19] with two equivalents of S-methylhydrazinecarbodi thioate[20] gave compound 1 having the molecular formula ($C_{18}H_{26}N_4O_{10}S_4$). Elemental analyses, physical properties, and IR data are listed in Table 1.

The IR spectrum of 1 showed stretching vibration bands at 3220 (N-H), 1760 cm^{-1} (OAc) and two medium intensity bands



R	Compound No.
CH_3	(1,3,5)
$CH_2C_6H_5$	(2,4,6)

Scheme I

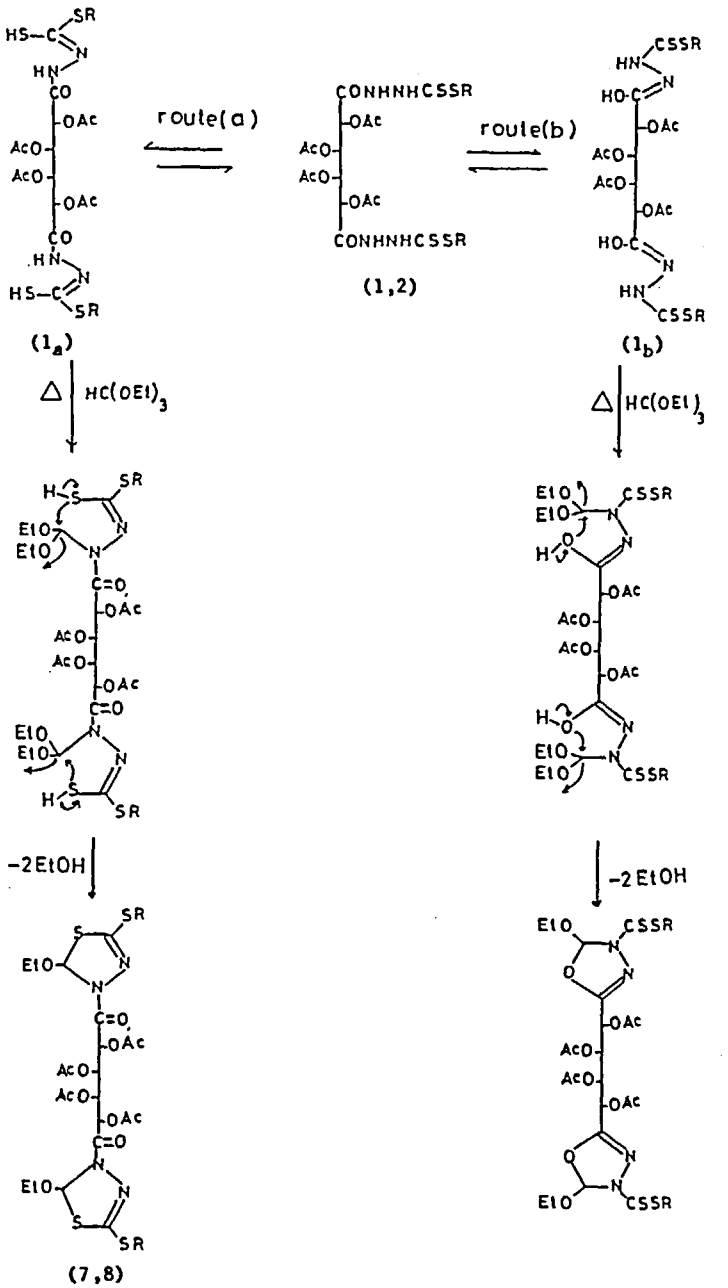
at 1655 and 1525 cm^{-1}, which are due to amide band-I stretching and amide band-II deformation, respectively.[21] Finally, bands were observed at 1480 and 1440 cm^{-1} due to the thioamide band-I and thioamide band-II, respectively.

The ^{1}H-NMR spectrum of compound 1 (DMSO-d_6) gave four pairs of singlets (Table 1) : δ 2.00 and 2.15 ppm (12H, 4 O-Ac), 2.42 and 2.49 ppm (6H, 2S-CH_3), 5.08 (2H, H-2, H-5) and

TABLE 1. Physical Properties, Elemental Analysis and Spectral Data of Compounds (1-8).

Cpd. No.	mp °C	Yield %	Molec.Formula	Analysis %C	Analysis %H	Analysis %N	IR-Spectral Data (cm^{-1}) OAc	N-H	Amide-I/ Amide-II	thioamide-I/ thioamide-II	^{1}H NMR Chemical Shifts (δppm) in $CDCl_3$ (Cpd.1,2 in DMSO-d_6) (OAc)*	(C-H)**	(SCH_3)*	SCH_2/ Ph	(N-H)	
1	230	70	$C_{18}H_{26}N_4O_{10}S_4$	36.85 37.28	4.44 4.65	9.55 9.43	1760	3220	1655 1525	1480 1440	2.00 2.15	5.08 5.50	2.42 2.49		10.67 11.31	
2	116	83	$C_{30}H_{34}N_4O_{10}S_4$	48.78 48.35	4.61 4.37	7.59 7.91	1760	3200	1675 1515	1480 1425	1.85 2.08	5.02 5.48		4.33,4.46 (2s,4H) 7.12,7.36 (m,10H)	10.68 11.36	
3	242	51	$C_{18}H_{22}N_4O_8S_4$	39.27 39.08	4.00 4.06	10.18	1760	C=N 1535			2.06 2.14	5.70 6.28	2.72			
4	182	58	$C_{30}H_{30}N_4O_8S_4$	51.28 51.10	4.27 4.52	7.98	1760	1525			1.86 1.98	5.55 6.12		4.34(s,4H) 7.15-7.23 (m,10H)		
5	107	73	$C_{18}H_{22}N_4O_{10}S_2$	41.69 42.01	4.25 3.95	10.81	1755	1570			2.07 2.13	5.72 6.25	2.74			
6	135	70	$C_{30}H_{30}N_4O_{10}S_2$	53.73 53.57	4.48 4.36	8.36	1770	1560			2.05 2.12	5.67 5.90		4.47(s,4H) 7.16-4.40 (m,10H)		(Thiadiazoline proton)**
7	197	64	$C_{24}H_{34}N_4O_{12}S_4$	41.26 41.61	4.87 4.90	8.02	1765	1540	C=O 1700		1.99 2.14	5.58 5.78	2.66		OCH_2-CH_3 3.50 1.19 (q,4H)(t,6H)	7.22
8	212	69	$C_{36}H_{42}N_4O_{12}S_4$	50.82 51.02	4.94 4.78	6.59	1760	1550	1700		1.90 2.12	5.70 5.86		4.43(s,4H) 7.20-7.45 (m,10H)	3.42 1.14 (q,4H)(t,6H)	7.12

* Each value is (s,6H), ** Each value is (s,2H).



R	Compound No.
CH_3	(1,7)
$CH_2C_6H_5$	(2,8)

Scheme II

5.50 ppm (2H, H-3, H-4), and two broad singlets, due to the four imino protons at δ 10.67 and 11.31 ppm. The above data is consistent with the structure of compound 1 as 2,3,4,5-tetra-O-acetylgalactaric acid bis[methylthio(thiocarbonyl)]-hydrazide.

Compound 1 gave a reddish coloration, when treated with methanolic ferric chloride solution, which suggests the thioamide N-H protons are tautomeric and could, therefore, be responsible for either or both of the tautomeric forms (1a and 1b) (Scheme II). This tautomerism was established by the appearance of two SCH_3 singlets in the ^{1}H-NMR spectrum (DMSO-d_6), presumably due to the Lewis basic character of DMSO. Recording the spectra in the non-basic solvent, $CDCl_3$, gave only one S-CH_3 singlet (δ2.41 ppm).

The condensation of 2,3,4,5-tetra-O-acetylgalactaroyl dichloride with S-benzylhydrazinecarbodithioate[22] produced 2,3,4,5-tetra-O-acetylgalactaric acid bis[benzylthio(thiocarbonyl)hydrazide] (2) (Table 1).

Dehydrative cyclisation of compound 1, using phosphorous oxychloride, gave compound 3 having a molecular formula ($C_{18}H_{22}N_4O_8S_4$). Its physical properties and spectral data are listed in Table (1). The product gave no coloration with ferric chloride solution, indicating absence of the four hydrazido-protons found in the parent bis(hydrazide).

Spectral data (Table 1) are in agreement with structure 3 namely, 1,2,3,4,-tetra-O-acetyl-1,4-bis(5-S-methyl-1,3,4-thiadiazol-2-yl)galacto-tetritol. Similarly, the saccharide bis(hydrazide) 2, reacted under the same cyclisation conditions, gave 1,2,3,4-tetra-O-acetyl-1,4,-bis(5-S-benzyl-1,3,4-thiadiazol-2-yl)galacto-tetritol (4).

Dehydrosulfurization of compound 1 occurred when heating with thionyl chloride (in DMF) to give compound 5. Its elemental analysis agreed with molecular formula ($C_{18}H_{22}N_4O_{10}S_2$), a product with two molecules of hydrogen sulfide less than the parent bis(hydrazide) 1.

Spectral data (Table 1) are in agreement with structure (5), 1,2,3,4-tetra-O-acetyl-1,4-bis(5-methyl-1,3,4-oxadiazol-2-yl)galacto-tetritol. A similar treatment of saccharide-bis-(hydrazide) 2 with thionyl chloride gave 1,2,3,4-tetra-O-acetyl-1,4-bis(5-benzyl-1,3,4-oxadiazol-2-yl)galacto-tetritol (6).

Finally, treating saccharide-bis(hydrazide) 1 with triethyl orthoformate, gave the cyclic compound 7 of molecular formula ($C_{24}H_{34}N_4O_{12}S_4$).

The structure given for 7 as 3,3'-(2,3,4,5-tetra-O-acetylgalactar-1,6-dioyl)bis[(2-ethoxy-2,3-dihydro-5-S-methyl)-1,3,4-thiadiazole], is supported by spectral data (Table 1). Employing the same cyclising conditions to saccharide bis-(hydrazide) 2, yielded 3,3'-(2,3,4,5-tetra-O-acetylgalactar-1,6-dioyl)-bis[(2-ethoxy-2,3-dihydro-5-S-benzyl)-1,3,4-thia-diazole] (8). A mechanism for the latter cyclisation reaction is postulated in scheme II.

Scheme (II) indicates mechanistic pathway (a) involving thione-thiol interconversion rather than the more difficult keto-enol tautomerism.

EXPERIMENTAL

General Procedures : Melting points were determined with a Kofler-Block and are reported uncorrected. The infra-red spectra were recorded as potassium bromide discs recorded

on a Pye Unicam SP1025 and/or SP2000 spectrophotometer. ^{1}H-NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer, using $(Me)_4$ Si as an internal standard. TLC was performed on silica-gel G (Merck) with a mixture of chloroform-methanol as the elution solvent. Iodine vapour was used to visualize compounds. The microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo and/or Alexandria University.

Preparation of Saccharide-bis(hydrazides)(1) and (2). A solution of S-methyl (or S-benzyl) hydrazinecarbodithioate (0.01 mol) in 20 mL of dimethylacetamide, was added, with stirring, to a solution of 2,3,4,5-tetra-O-acetyl galactaroyl dichloride (0.005 mol) in 10 mL dimethylacetamide. The reaction mixture was stirred for one h at room temperature, then poured into ice-water, the product removed by filtration and recrystallized from methanol.

Cyclisation of 1 or 2 Using Phosphorous Oxychloride. Dry saccharide-bis(hydrazide) 1 or 2 (0.001 mol) was heated with phosphorous oxychloride (10 mL) until complete dissolution occured (20 min). The mixture was then cooled, diluted with a cold saturated solution of $NaHCO_3$ (200 mL), extracted with $CHCl_3$, washed with water, dried, and concentrated. The product was recrystallized from ethanol.

Cyclisation of 1 or 2 Using Thionyl Chloride. A solution of compound 1 or 2 (0.001 mol), in N,N-dimethylformamide (10 mL), was treated with thionyl chloride (10 mL). The mixture was heated for 10-15 min on a boiling water bath, then concentrated, cooled, and diluted with a cold saturated solution of $NaHCO_3$ (200 mL). The solid product that separated out, was washed with water, and recrystallized from ethanol.

Cyclisation of 1 or 2 Using Triethyl Orthoformate. Dry saccharide-bis(hydrazide) 1 or 2 (0.001 mol) was refluxed with triethyl orthoformate (10 mL) until complete dissolution occurred (12 h). The reaction mixture was concentrated and the residue crystallized from methanol.

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