Note

Synthesis and reactions of 2-methyl-5-(D-arabino-tetrahydroxybutyl)-3-pyrrolecarbohydrazide

Mohamed El Sadek*, Samy A. Abdel-Baky, and Nagwa N. El Soccary Chemistry Department, Faculty of Science, Alexandria University, Alexandria (Egypt) (Received August 28th, 1990; accepted for publication, in revised form, July 22nd, 1991)

The present work is a continuation of our work on the synthesis of heterocyclic compounds from saccharide derivatives¹⁻⁸. Ethyl 2-methyl-5-(D-*arabino*-tetrahydroxy-



Scheme 1

0008-6215/92/\$05.00 © 1992 - Elsevier Science Publishers B.V. All rights reserved.

^{*} To whom correspondence should be addressed.

butyl)-3-pyrrolecarboxylate (1, Scheme 1) was heated under reflux with hydrazine hydrate to give 2-methyl-5-(D-*arabino*-tetrahydroxybutyl)-3-pyrrolecarbolate hydrazide (2) in 89% yield. The structure was confirmed by elemental analysis and by the fact that the i.r. spectrum of 2 showed appropriate absorbances for the amide, hydroxy, and amino functions (for details, see Experimental section).

Treatment of hydrazide 2 with various aromatic aldehydes in acidic medium afforded the corresponding aldehyde acylhydrazones 3-11 in 62-95% yields (Scheme 1). The structures of these hydrazones were established by i.r. and 'H-n.m.r. spectroscopy, wherein the C = N, CONH, NH, and OH bands appeared at the expected frequencies and all protons showed appropriate resonances in their 'H-n.m.r. spectra (for details, see Experimental section). Compounds 3-11 all gave satisfactory elemental analyses (Table I), and the structures were confirmed by 'H-n.m.r. spectroscopy (for details, see Experimental section).

TABLE I

Compound no.	М.р . (°)	Yield (%)	Solvent ^a	R*	Molecular formula	Anal. Co	alc./Found	
	()	(,,,,			Jonna	С	Н	Ν
3	88	89.5	1:1 E-B	0.58	$C_{17}H_{21}N_{3}O_{5}$	58.77	6.05	12.10
						59.02	6.10	11.80
	104	85	E	0.24	$C_{17}H_{20}ClN_{3}O_{5}$	53.45	5.24	11.01
						53.23	5.41	11.10
5	122	82	Е	0.59	$C_{12}H_{20}ClN_3O_5$	53.45	5.24	11.01
						53.64	5.19	11.22
6	97	91	2:1 E-B		$C_{18}H_{23}N_{3}O_{6}$	57.27	6.10	11.14
					10 25 5 0	56.99	6.40	11.30
7	115	93	2:1 E-B	0.40	$C_{12}H_{11}N_{3}O_{6}$	56.18	5.78	11.57
					17 21 3 0	56.12	5.84	11.50
8	197	95	2:1 EB	0.40	$C_{12}H_{20}N_{1}O_{2}$	52.02	5.10	14.28
					17 20 4 7	52.37	5.22	13.97
9	95	92	Е	0.41	$C_{10}H_{22}N_2O_5$	61.10	6.16	11.26
					17 25 5 5	61.30	6.19	11.09
10	102	62	2:1 E-B		$C_1 H_1 N_2 O_1$	53.40	5.64	12.46
					10 10 8-3	53.68	5.46	12,59
11	110	73	2:1 E-B		C.H.N.O.S	50.97	5.38	11.89
					- 1519- 130 50	51.02	5 14	12.00

Yields and physicochemical and analytical data for compounds 3-11

^{*a*} E, EtOH; B, PhH. ^{*b*} Solvent: 5:1 CHCl₃–MeOH.

When hydrazones 8–11 were boiled with acetic anhydride (Scheme 2) for one hour, these compounds were converted to the N^1 -acetyl-3-(5-aryl- N^4 -acetyl-1,3,4-oxa-diazolin-2-yl)-2-methyl-5-(D-*arabino*-tetraacetoxybutyl)pyrroles (12–15), which were all isolated in crystalline form in yields ranging from 62 to 69% (Table II). The structures of 12–15 were confirmed by i.r. (see Experimental section) and ¹H-n.m.r. spectroscopy (Table III) and by elemental analyses (Table II).

TABLE II

Compound	M . p .	Yield	Molecular	Anal. Co	alc./Found	
<i>no</i> .	()	(20)	Jormula	C	H	N
12	132	62	$C_{29}H_{32}N_4O_{13}$	54.04	4.97	8.70
				54.12	5.04	8.48
13	179	67	$C_{31}H_{35}N_{3}O_{11}$	59.52	5.60	6.72
				59.58	5.82	6.49
14	195	64	$C_{27}H_{31}N_{3}O_{12}$	55.02	5.26	7.13
			27 51 5 12	55.13	5.18	7.14
15	205	69	$C_{22}H_{21}N_2O_{11}S^a$	53.55	5.12	6.94
			27 51 5 11	53.89	5.12	7.01
16	80	72		52.93	5.04	11.76
			21 24 4 9	53.20	5.00	11.59
17	97	75	C ₁₂ H ₁₇ N ₁ O ₇	60.37	5.91	9.19
			- 23 21 3 - 1	60.42	6.02	9.08

Yields, melting points, and analytical data for compounds 12-17

^a Calc.: S, 5.29; found: S, 5.08.

TABLE III

¹H-N.m.r. spectral data for the 3-(1,3,4-oxadizolin-2-yl)pyrroles 12, 13, and 15

Compound	Chemic	al shift (p.p.m.))					
no."	CH ₃	OAc	NAc	Sugar-H	= <i>CH</i>	Ar	ArCH	•
12	1.9	2.1-2.4	2.4	3.9-5.3	6.5	8.0-8.3	10.1	
13 ^b	1.4	2.0-2.1	2.4	3.9-5.3	6.6	7.2-7.3	9.3	
15	1.7	2.0-2.4	2.7	3.6-5.2	6.9	7.3-8.0	9.9	

^a For structures, see Scheme 2. ^b Resonances of -CH = CH- are at 6.7 (d) and 7.4-7.5 (t) p.p.m.



Scheme 2



TABLE IV

Yields and physicochemical and analytical data for compounds 18-24

Compound	M.p.	Yield	R _F ^a	Molecular	Anal.	Calc./Fe	ound
n0.	(")	(%)		Jormula	C	H	N
18	145	75	0.84	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46
19	115	50	0.83	C ₁₄ H ₁₂ ClN ₃ O ₂ ^b	66.01 58.04	4.90 4.17	16.50 14.50
20	165	47	0.93	$C_{14}H_{12}ClN_{3}O_{2}^{c}$	57.90 58.04	4.20 4.17	14.77 14.50
21	200	63	0.77	$C_{15}H_{15}N_{3}O_{3}$	58.10 63.15	4.14 5.30	14.37 14.73
22	175	70	0.83	C ₁₄ H ₁₃ N ₃ O ₃	63.22 61.99	54.46 4.83	14.34 15.49
23	198	79	0.67	C. H. N.O.	61.94 56.00	4.97 4.03	15.50 18.66
23	100	00	0.07	$C_{14}H_{12}H_{4}O_{4}$	56.20	3.95 5.37	18.69
24	163	80	U.//	$C_{16}n_{15}N_{3}O_{2}$	68.52	5.07	15.21

"Solvent: 3:2 EtOAc-hexane. ^bAnal. Calc. Cl, 12.26; found Cl, 12.11. ^cAnal. Calc. Cl, 12.26; found Cl, 12.60.

Deacetylation^{9,10} of compounds **12** and **13** with 3% sodium methoxide in methanol (Scheme 2) afforded the deacetylated products **16** and **17**, which were identified by their i.r. and ¹H-n.m.r. spectra (for details, see Experimental section) and confirmed by elemental analysis (Table II).

Periodate oxidation of hydrazones 3–9 afforded the corresponding pyrrole aldehydes 18–24 (Scheme 3) in yields of 47–80% (Table IV). These compounds were recognized by the conspicuous absence of OH absorbances in their i.r. spectra, with the appearance of pyrrole-CHO absorbances in the 1655–1670 cm⁻¹ region. The presence of the CHO group was further confirmed by a resonance at δ 9.35 in the ¹H-n.m.r. spectra. (For details, see the Experimental section).

Condensation of compounds **18–24** with a number of aroylhydrazines furnished the corresponding derivatives **25–59** (Scheme 3, Table V). The latter set of compounds were characterized by i.r. and ¹H-n.m.r. spectroscopy (for details of representative examples, see Experimental section) and by elemental analyses (Table V).

Three of the acylhydrazones, compounds 42, 46, and 50, were heated under reflux with acetic anhydride for one hour to give the triheterocyclic derivatives 60–62 (Scheme 4). The structures of these compounds were confirmed by i.r. spectroscopy (disappearance of NH bands, with appearance of characteristic NAc absorbances), and by ¹H-n.m.r. spectroscopy, whereby all the protons could be definitively assigned (for details, see Experimental section). In addition, 61 showed a molecular ion in its mass spectrum at m/z 591, with a base peak at m/z 139.



Scheme 4

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block and are uncorrected. I.r. spectra were recorded for samples in a KBr matrix on a Unicam SP 1025 spectrometer, and the ¹H-n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) spectrometer. Electron-impact mass spectra were obtained at 70 eV on a Hewlett–Packard 5988A mass spectrometer. Thin-layer chromatography was carried out on

Yields and physic	sochemical and	i analytical data	for compounds 25-62					
Compound	M.p.	Yield	Molecular	Anal. Calc	./Found			
NO.	0	(0%)	Jormua	С	Н	N	cı	
25	250	68	C ₁ ,H ₁₈ CIN,O,	61.84	4.45	17.17	8.69	
			4 9 9	62.03	4.27	17.12	8.38	
26	216	60	$C_{22}H_{21}N_5O_2$	68.20	5.46	18.08		
				68.32	5.47	18.02		
27	212	65	$C_{22}H_{21}N_{5}O_{3}$	65.50	5.25	17.36		
				65.81	5.17	17.40		
28	228	73	$C_{21}H_{18}N_6O_4$	60.28	4.34	20.09		
				60.61	4.09	20.10		
29	237	62	$C_{20}H_{18}N_6O_2$	64.16	4.85	22.45		
				64.22	4.66	22.51		
30	218	73	C ₂₁ H ₁₈ CIN ₅ O ₂	61.84	4.45	17.17	8.69	
			, ,	62.03	4.47	17.35	8.71	
31	237	65	C,,H,,CIN,O,	62.63	4.78	16.60	8.40	
			• •	62.53	4.93	16.47	8.71	
32	240	59	$C_{22}H_{20}CIN_{5}O_{3}$	60.35	4.60	15.99	8.10	
				60.23	4.84	15.89	8.22	
33	252	72	C ₂₁ H ₁ ,CIN ₆ O ₄	55.70	3.78	18.56	7.83	
				55.80	3.56	18.72	7.48	
2	255	64	C ₂₀ H ₁ ,CIN ₆ O ₂	58.76	4.19	20.56	8.67	
				59.02	4.41	20.23	8.71	
35	203	12	C ₂₁ H ₁₈ CIN ₅ O ₂	61.84	4.45	17.17	8.69	
				62.01	4.24	17.20	8.37	
36	219	69	$C_{22}H_{20}CIN_5O_2$	62.63	4.78	16.60	8.40	
				62.92	4.37	16.50	8.53	
37	230	62	$C_{22}H_{20}CIN_{5}O_{3}$	60.35	4.60	15.99	8.10	
				60.51	4.38	16.30	8.07	
38	206	74	C ₂₁ H ₁₇ CIN ₆ O ₄	55.70	3.78	18.56	7.83	
				55.92	3.48	18.72	7.66	
39	217	63	$C_{20}H_{17}CIN_{6}O_{2}$	58.76	4.19	20.56	8.67	
				59.03	4.14	20.51	8.70	
40	207	67	$C_{22}H_{21}N_5O_5$	65.50	5.25	17.36		
				65.67	5.20	17.06		
41	244	74	$C_{22}H_{20}CIN_{s}O_{3}$	60.35	4.60	15.99	8.10	
				60.09	4.53	16.32	8.13	

316

TABLE V

•

::) :

42	220	61	C ₂₃ H ₂₃ N ₅ O ₃	66.17 66.20	5.55 5.57	16.78 16.60	
43	245	76	C ₂₂ H ₂₀ N ₆ O ₅	58.93 58.67	4.50	18.74	
44	234	66	C ₂₁ H ₂₀ N ₆ O ₃	62.37	4.98	20.78	
45	223	70	C.H. N.O.	62.38 64 77	5.03 4 97	20.46 17 98	
2		2	221-25-29	64.71	4.90	18.02	
46	241	72	C ₂₁ H ₁₈ CIN ₅ O ₃	59.50	4.28	16.52	8.36
ţ		a,		59.13	4.27	16.84	8.16
47	202	69	C ₂₂ H ₂₁ N ₅ O ₃	65.50 55 83	5.25	17.36	
48	200	76	C,,H ₁₈ N ₆ O	63.85 58.06	4.18	11.42	
			2 2 3	58.13	4.09	19.41	
49	198	68	C ₂₀ H ₁₈ N ₆ O ₃	61.53	4.65	21.53	
				61.82	4.90	21.27	
8	220	74	C ₂₁ H ₁₈ N ₆ O ₄	60.28 50.05	4.34	20.09	
5	110	5		06.60	10.4	20.12	5
10	214	10		55.93	3.78 3.49	18.72	7.48
52	228	71	C.,H.,N,O,	61.11	4.66	19.43	
				61.32	4.38	19.65	
53	230	6 4	$C_{22}H_{20}N_6O_5$	58.93	4.50	18.74	
				58.63	4.58	19.02	
X	210	63	$C_{20}H_{17}N_{7}O_{4}$	57.28	4.09	23.38	
				57.30	4.02	23.09	
55	219	76	C ₂₃ H ₂₁ N ₅ O ₂	69.16	5.30	17.53	
				69.21	5.08	17.49	
3 6	223	75	C ₂₃ H ₂₀ CIN ₅ O ₂	63.67	4.65	16.14	8.17
-		ļ		63.90	4.52	16.21	8.08
SI	215	74	C ₂₄ H ₂₃ N ₅ O ₂	69.72	5.61	16.94	
:		i		70.02	5.43	17.02	
38	220	78	C ₂₃ H ₂₀ N ₆ O ₄	62.16	4.54	18.91	
				62.17	4.27	19.05	
59	263	72	C ₂₂ H ₂₀ N ₆ O ₂	65.99	5.03	20.99	
				66.03	4.90	20.98	
60	245	52	C ₂₇ H ₂₄ N ₆ O,	59.54	4.41	15.44	
				59.91	4.52	15.09	
. 19	256	- 19	C ₂₉ H ₂₉ N ₅ O ₆	64.07	5.34	12.89	
				64.30	5.38	12.45	
62	204	70	C ₂₉ H ₂₆ CIN ₅ O ₇	58.82	4.39	11.83	6.00
				58.51	4.40	12.01	6.10

NOTE

317

silica gel plates from Analtech. Microanalyses were performed at the Faculty of Science, Cairo University (Cairo, Egypt).

2-Methyl-5-(D-arabino-tetrahydroxybutyl)-3-pyrrolecarbo hydrazide (2). — Ethyl 2-methyl-5-(D-arabino-tetrahydroxybutyl)-3-pyrrolecarboxylate (1, 10 g, 40 mmol) was heated under reflux with hydrazine hydrate (20 mL, 400 mmol) for 1 h. The mixture was then poured into cold EtOH, and the product that precipitated was filtered, washed with EtOH (3 ×), dried, and crystallized from 2:1 EtOH–H₂O to give needles of **2** (9.1 g, 89%): m.p. 185°; R_F 0.22 (5:1 CHCl₃–MeOH); i.r. 1640 (CONH), 3200 (NH), and 3450 cm⁻¹ (OH).

Anal. Calc. for $C_{10}H_{17}N_3O_5$: C, 46.33; H, 6.61; N, 16.21. Found: C, 46.40; H, 6.56; N, 16.20.

N-[2-Methyl-5-(D-arabino-tetrahydroxybutyl)-3-pyrroloyl] aldehyde hydrazones (3-11). — To solution of compound 2 (2.0 g, 7.7 mmol) in EtOH (20 mL) containing acetic acid (0.1 mL) was added the appropriate aldehyde (7.7 mmol), and the mixture was heated under reflux for 1 h. The aldehyde hydrazone derivative that precipitated was filtered, washed with EtOH (5 mL), dried, and crystallized from the appropriate solvent or solvent mixture (Table I). Physicochemical and analytical data are provided in Table I. ¹H-N.m.r. data (Me₂SO-d₆) for 3 and 8: δ 2.45 (s, 3 H, CH₃ at C-2), 3.25–4.90 (m, 5 H, sugar C–Hs), 6.5 (s, 1 H, CH at C-4), 7.35–8.23 (m, 4 or 5 H, aryl), 8.35–8.60 (s, 1 H, C = NH), 10.9–11.1 (s, 1 H, NH), and 11.03–11.25 (s, 1 H, NHCO).

 N^{1} -Acetyl-3-(N^{4} -acetyl-5-aryl-1,3,4-oxadiazolin-2-yl)-2-methyl-5-(D-arabinotetraacetoxybutyl)pyrroles (12–15). — Aryl aldehydrazones 8–11 (300 mg) were each boiled with Ac₂O (15 mL) for 1 h, and the mixture was then poured onto crushed ice (200 g), whereby the oxadiazoline derivatives 12–15 precipitated. The compounds were isolated by filtration, washed thoroughly with H₂O, dried, and crystallized from EtOH as needles: i.r. 1600–1610 (C = N), 1640–1650 (NAc), and 1710–1735 cm⁻¹ (OAc). For yields and physicochemical and analytical data, see Table II; for ¹H-n.m.r. data, see Table III.

 N^1 -Acetyl-3-(N^4 -acetyl-5-aryl-1,3,4-oxadiazolin-2-yl)-2-methyl-5-(D-arabinotetrahydroxybutyl)pyrroles (16 and 17). — A solution of 12 or 15 in 3% NaOMe in MeOH (10 mL) was left standing overnight. Amberlite IR-120 [H⁺] resin (5 g) was added until the solution was neutral, whereby the oxazoline derivative precipitated. The product was filtered, washed with EtOH, dried, and crystallized from EtOH. I.r. data: 1600 (C = N), 1640–1650 (NAc), and 3360–3450 cm⁻¹ (OH); ¹H-n.m.r. data (Me₂SO-d₆) for 16: δ 1.9 (s, 3 H, CH₃ at C-2), 2.4 (s, 3 H, NAc), 3.3–3.9 (m, 5 H, sugar C–Hs), 6.5 (s, 1 H, pyrrole C-4), 8.0–8.3 (2 d, 4 H, Ar), and 9.5 (s, 1 H, CH oxadiazoline). For analytical and physicochemical data, see Table II.

N-(5-Formyl-2-methyl-3-pyrroloyl)aldehyde hydrazones (18–24). — To a solution of the appropriate aldehyde hydrazone 3-9 (11 mmol) in distilled H_2O (50 mL) was added dropwise, with stirring, aqueous NaIO₄ (34 mmol, 50 mL). The mixture was stirred for 5 h, and the formyl derivative which separated was filtered, washed with water, dried, and crystallized from EtOH to give 18–24. For physicochemical and analytical data, see Table IV. I.r. data: 1590–1605 (C=N), 1640–1650 (CONH),

1655–1670 (CHO), and 3200–3400 cm⁻¹ (NH); ¹H-n.m.r. data for a typical formyl derivative (Me₂SO- d_6); δ 2.41 (s, 3 H, CH₃ at C-2), 6.55 (s, 1 H, H-4), 7.83–8.15 (2 d, 4 or 5 H, Ar), 8.32 (s, 1 H, CH = N), 9.35 (s, 1 H, CHO), 11.1 (s, 1 H, NH), and 11.25 (s, 1 H, NHCO).

N-[5-(Aroylhydrazonomethyl)-2-methyl-3-pyrroloyl]aldehyde hydrazones (25– 59). — To a solution of the appropriate aldehyde hydrazone 18–24 (1 mmol) in EtOH (10 mL) containing HOAc (0.01 mL) was added the appropriate aroylhydrazine (1 mmol) in EtOH (5 mL). The mixture was heated under reflux for 1 h, whereby the hydrazone derivative separated upon cooling. The product was filtered, washed with EtOH (5 mL), and crystallized from 2:1 PhH–EtOH. For yields and physicochemical and analytical data, see Table V. ¹H-n.m.r. data (Me₂SO-d₆) for 40: δ 2.45 (s, 3 H, Me), 3.7 (s, 3 H, MeO), 6.95 (s, 1 H, = CH pyrrole), 7.45–7.80 (m, 9 H, ArHs), 8.15 (s, 1 H, pyrrole-CH =), 8.30 (s, 1 H, p-(MeO)C₆H₄CH =), 11.50–11.70 (s, 2 H, N–NH). Analogues of 40 showed similar ¹H-n.m.r. spectra.

N¹-Acetyl-3-(N⁴-acetyl-5-aryl-1,3,4-oxadiazolin-2-yl)-5-(N⁴-acetyl-2-aryl-1,3,4-oxadiazolin-2-yl)-2-methylpyrroles (**60–62**). — Hydrazone compounds **42**, **46**, and **50** (1 mmol) were each boiled in acetic anhydride (5 mL) for 1 h, and the mixture was poured onto ice (200 g). The products that separated were filtered, washed with H₂O, dried, and crystallized from 2:1 PhH–EtOH. For yields and physicochemical data see Table V. I.r. data: 1605–1610 (C = N), 1650–1655 (NAc), and 1760 cm⁻¹ (OAc); ¹H-n.m.r. data (CDCl₃) for **61**: δ 2.03 (s, 3 H, pyrrole-CH₃), 2.15 (s, 3 H, OAc), 2.3 (s, 3 H, NAc), 7.0 (s, 1 H, pyrrole-CH =), 7.05–7.35 (m, 8 H, Ar), 7.65 and 7.75 (2 s, 2 H, 2 × CH).

REFERENCES

- 1 H. El Khadem, M. M. El Sadek, and M. H. Meshreki, J. Chem. Soc. C, (1968) 2097-2099.
- 2 H. El Khadem, Z. M. El Shafei, E. H. El Ashry, and M. M. El Sadek, Carbohydr. Res., 49 (1976) 185-193.
- 3 M. M. El Sadek, Pharmazie, 37 (1982) 357-359.
- 4 M. M. El Sadek, M. A. Mostafa, M. M. Abdel Rahman, and N. B. Zagzoug, Bratislava Symposium on Saccharides, Smolenice, Czechoslovakia, (1984) 67.
- 5 M. M. El Sadek, C. D. Warren, and R. W. Jeanloz, Carbohydr. Res., 100 (1982), 35-38.
- 6 M. M. El Sadek, M. El Essawi, and S. A. Abdel-Baky, J. Chem. Eng. Data, 26 (1987) 1277-1279.
- 7 M. M. El Sadek, G. A. Yacout, and N. N. El Soccary, Pak. J. Sci. Ind. Res., 32 (1989) 649-654; Chem. Abstr., 114: 62010j.
- 8 M. M. El Sadek, H. M. Faidallah, and S. Y. Hassan, Carbohydr. Res., 199 (1990) 248-254.
- 9 F. García González and A. Gómez Sánchez, Adv. Carbohydr. Chem., 20 (1965) 303-355.
- 10 G. Zemplén, and A. Kunz. Ber., 56B (1923) 1705-1710.