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Note

Sugar (lepidin-2-yl)hydrazones and synthesis of 1-(alditol-1-yl)-5-methyl[1,2,4]triazolo[4,3-*a*]quinoline

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Heterocycles that incorporate the quinoline nucleus exhibit various biological activities[1–10]. Thus [1,2,4]triazolo[4,3-*a*]quinolines have been found to be active against *Piricularia oryzae*[11] and are used as agricultural bactericides and fungicides. Some possess other antimicrobial activity[12], and some are useful as dyestuff intermediates[13].

In continuing our work on the synthesis of carbohydrate derivatives of biologically active polycondensed heterocycles[14–16] and of *C*-nucleoside analogues[17], we report herein the synthesis of 1-(alditol-1-yl)-5-methyl[1,2,4]triazolo[4,3-*a*]quinoline.

Frequently employed methods[18–24] for constructing the [1,2,4]triazolo[4,3-*a*]quinoline utilize 2-hydrazinoquinoline and its derivatives. The selected starting material for this study was 2-hydrazinolepidine [2-hydrazino-4-methylquinoline (**1**)], which was prepared from 2-hydroxylepidine by sequential chlorination with phosphorus oxychloride, and then reaction with hydrazine[25,26]. Condensation of **1** with a number of monosaccharides **2a–d** gave the respective hydrazones **3a–d**. Crystalline hydrazones **3a–d** could be obtained from D-galactose, D-mannose, D-arabinose, and D-xylose. Acetylation of **3a**, **3c**, and **3d** with acetic anhydride in pyridine gave, respectively, the acetyl derivatives **6e–g**. The IR spectra of **6e–g** showed two absorption bands in the carbonyl frequency region (Table III). The ^{1}H NMR spectrum of **6e** confirmed the presence of an NAc group (δ 2.33), in addition to the five OAc groups that appeared as five singlets. The doublet at low field (δ 6.44) was assigned to H-1, followed by the rest of the alditol-1-yl side chain at higher field. The spectrum of **6f** showed a similar pattern.

Dehydrogenation of **3a** and **3b** to **5a** and **5b** was carried out by the action of iron(III) chloride in ethanolic solution. The oxidation of **3a** and **3b** may take place

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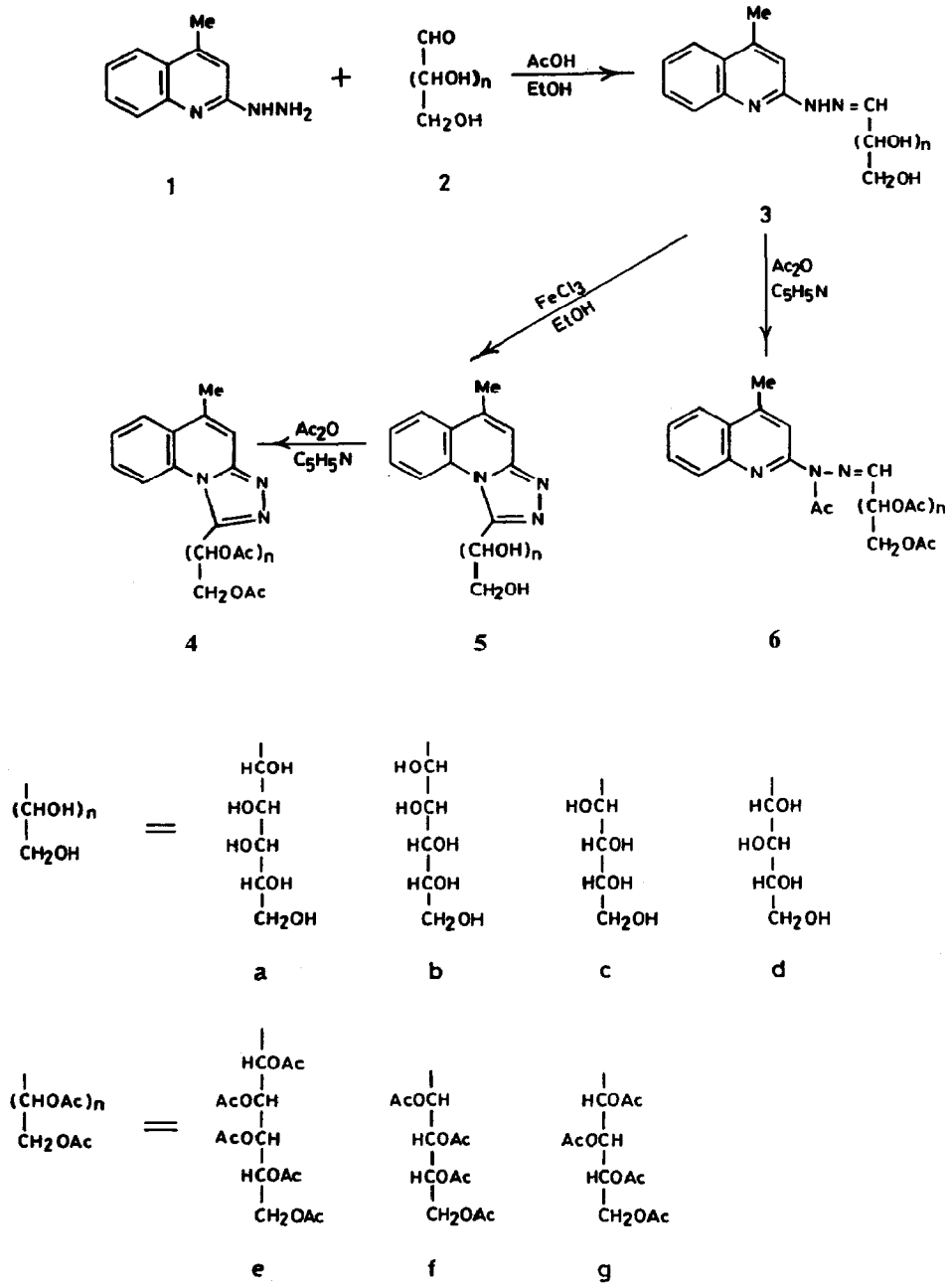

Scheme 1.

by the electrophilic attack of the hard acid site of iron(III) chloride[27] on the hardest basic site of **3a** and **3b**, followed by elimination of hydrogen chloride and formation of possibly a nitrilimine that undergoes a 1,5-electrocyclisation to give **5a**

TABLE I

^{1}H NMR spectral data for compounds **4e**, **5a**, **6e**, and **6f**

^{1}H Assignment	Chemical shift (δ)/Coupling constant (Hz)			
	4e [a]	**5a**	**6e**	**6f**
Alditolyl protons				
H-1	6.94(d)	5.84(s)	6.44(d)	6.57(d)
$J_{1,2}$	3.6		2.8	4.2
H-2	5.86(dd)	4.20(d)	5.47(t)	5.52(t)
$J_{2,3}$	9.1		4.2	4.8
H-3	5.73(dd)			5.43(t)
$J_{3,4}$	3.5	3.77(m)	5.32(m)	5.1
H-4	5.38(m)			5.22(m)
$J_{4,5}$	4.8			3.9
H-5	4.30(dd)		5.29(m)	4.16(dd)
$J_{5,5'}$	11.7	3.45(m)		12.0
H-5′	4.01(dd)			3.97(dd)
$J_{4,5'}$	7.5			6.6
H-6			4.13(q)	
H-6′			3.90(q)	
NAc			2.33(s)	2.35(s)
OAc	2.18(s)		2.08(s)	2.06(s)
OAc	2.15(s)		2.03(s)	2.01(s)
OAc	1.96(s)		2.00(s)	1.98(s)
OAc	1.81(s)		1.94(s)	1.96(s)
OAc	1.80(s)		1.92(s)	
OH's		5.70(bs)		
Quinoline protons				
	2.63(s)	2.72(s) Me	2.72(s)	2.73(s)
H-4	7.51(s)	7.79(s) H-3	7.18(s)	7.23(s)
H-6	8.11(d)	8.17(d) H-5	7.99(d)	7.99(d)
$J_{6,7}$	8.4	7.8 $J_{5,6}$	8.3	8.2
H-7	7.70(t)	7.81(t) H-6	7.76(t)	7.74(t)
H-8	7.90(t)	7.97(t) H-7	7.84(t)	7.84(t)
$J_{7,8}$	7.2	7.6 $J_{6,7}$	4.1	5.5
H-9	8.35(d)	8.69(d) H-8	8.18(d)	8.17(d)
$J_{8,9}$	8.3	8.5 $J_{7,8}$	8.2	8.3

[a] Quinoline protons showed the following long-range couplings; $J_{5,7}$ 1.5 Hz and $J_{6,8}$ 1 Hz.

and **5b**. Acetylation of **5a** gave the per-*O*-acetyl derivative **4e**. The IR spectrum of **4e** showed the presence of only one absorption in the carbonyl frequency region (OAc). The ^{1}H NMR spectrum showed the loss of two protons from precursor **3a** and confirmed the assigned structure **5a**.

By considering the magnitude of vicinal proton–proton coupling constants (where coupling constants are < 4 Hz for protons having gauche orientation, and the values > 7 Hz for those having antiparallel orientation) and by analogy with data for acetyl derivatives of acyclic carbohydrates, it was possible to deduce for **4e** the most preferred conformation[28]. Thus, for compound **4e** (Table I) the magni-

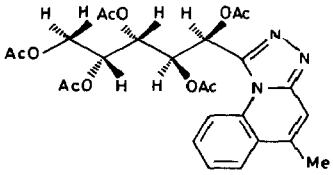

Fig. 1. The planar zig-zag conformation deduced for **4e**.

tude of $J_{1,2}$ (3.6 Hz) and $J_{3,4}$ (3.5 Hz) are relatively small, indicating a gauche relationship between H-1 and H-2 as well as between H-3 and H-4. The value of $J_{2,3}$ is large (9.1 Hz), indicating that H-2 and H-3 are antiparallel in the favoured conformer. The values for $J_{4,5}$ (4.8 Hz) and $J_{4,5'}$ (7.5 Hz) indicate the highest population of the conformer having H-5′ in an antiparallel orientation with H-4. Consequently, the planar zig-zag conformation (Fig. 1) could be given for **4e**.

EXPERIMENTAL

General methods.—Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Unicam SP 1025 Spectrometer. ^{1}H NMR spectra were measured with a Varian Gemini 200 Spectrometer for solutions in Me_2SO-d_6, except for **4e** measured in acetone-d_6. Elemental analyses were performed at the Microanalytical Laboratory, Cairo University.

Sugar (4-methylquinolin-2-yl)hydrazones (**3a–d**).—To a solution of 2-hydrazino-4-methylquinoline (**1**) (10 mmol) in EtOH (15 mL) was added the respective sugar **2a–d** (10 mmol) and acetic acid (0.1 mL). The mixture was heated under reflux on a water bath for 30 min. The solid that separated on cooling was filtered, washed with EtOH, and dried. The yellow product was crystallized from EtOH. See Table II for physicochemical data.

TABLE II

Microanalyses and IR spectral data for compounds **3a–d**

Compd	Yield (%)	mp (°C)	Molecular formula	Analysis (% Calcd/Found)			ν_{max}^{KBr} (cm^{-1})	
				C	H	N	NH/OH	C=N
3a	92	166–168	$C_{16}H_{21}N_3O_5$	57.3	6.3	12.5	3216	1613
				57.1	6.0	12.4		
3b	86	183–185	$C_{16}H_{21}N_3O_5$	57.3	6.3	12.5	3492,	1619
				57.4	6.4	12.5	3339	
3c	89	177–179	$C_{15}H_{19}N_3O_4$	59.0	6.3	13.8	3204	1615
				59.2	6.1	13.9		
3d	88	190–192	$C_{15}H_{19}N_3O_4$	59.0	6.3	13.8	3428,	1619
				59.1	6.1	13.8	3215	

TABLE III

Microanalyses and IR spectral data for compounds **6e–g**

Compd	Yield (%)	mp (°C)	Molecular formula	Analysis (%Calcd/Found)			ν_{max}^{KBr} (cm^{-1})	
				C	H	N	OAc	NAc
6e	83	197–199	$C_{28}H_{33}N_3O_{11}$	57.2	5.7	7.2	1746	1690
				57.2	5.7	7.4		
6f	85	184–186	$C_{25}H_{29}N_3O_9$	58.2	5.7	8.2	1740	1694
				58.2	5.6	8.6		
6g	82	172–174	$C_{25}H_{29}N_3O_9$	58.2	5.7	8.2	1738	1696
				58.3	5.7	8.5		

Per-O-acetyl-sugar [1-acetyl-1-(4-methylquinolin-2-yl)]hydrazones (**6e–g**).—A cold solution of **3a** or **3c** or **3d** (1.0 g) in dry pyridine (5 mL) was treated with Ac_2O (5 mL). The mixture was kept overnight at room temperature with occasional shaking. The mixture was poured onto crushed ice, and the product was collected by filtration, washed repeatedly with water, dried, and recrystallized from EtOH. See Table III for physicochemical data.

1-(Alditol-1-yl)-5-methyl[1,2,4]triazolo[4,3-a]quinoline (**5a** *and* **5b**).—A 2 M solution of iron(III) chloride in EtOH (2 mL) was added dropwise to a boiling solution of **3a** or **3b** (0.5 g) in EtOH (10 mL). Heating was continued for 10 min, and the mixture was then kept overnight at room temperature. The product was filtered, washed repeatedly with water, and dried. It was crystallized from EtOH as yellow needles. See Table IV for physicochemical data.

1-(Penta-O-acetyl-D-galactitol-1-yl)-5-methyl[1,2,4]triazolo[4,3-a]quinoline (**4e**). —A cold solution of **5a** (0.5 g, 1.5 mmol) in dry pyridine (3 mL) was treated with Ac_2O (3 mL), and the mixture was kept overnight at room temperature with occasional shaking. It was poured onto crushed ice, and the product was filtered, washed with water, and dried. It was crystallized from EtOH as colourless needles. See Table IV for physicochemical data.

TABLE IV

Microanalyses and IR spectral data for compounds **4e**, **5a**, and **5b**

Compd	Yield (%)	mp (°C)	Molecular formula	Analysis (%Calcd/Found)			ν_{max}^{KBr} (cm^{-1})		
				C	H	N	OH	OAc	C=N
4e	82	121–123	$C_{26}H_{29}N_3O_{10}$	57.5	5.4	7.7		1744	1610
				57.6	5.5	7.5			
5a	74	193–195	$C_{16}H_{19}N_3O_5$	57.6	5.7	12.6	3395		1631
				58.1	5.6	12.6			
5b	75	158–160	$C_{16}H_{19}N_3O_5$	57.6	5.7	12.6	3396		1629
				57.9	6.0	12.5			

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