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SYNTHESIS AND MASS SPECTRA OF SOME 2-METHYL- AND 2-PHENYL-5-(POLYACETOXYALKYL)-1,3,4-OXADIAZOLES AND THEIR CONFORMATIONS IN SOLUTION*

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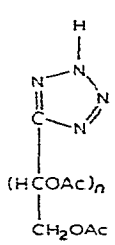
ABSTRACT

The synthesis and mass spectra of some 2-methyl- and 2-phenyl-5-(polyacetoxyalkyl)-1,3,4-oxadiazoles (**4–9**) are described. The preferred conformations of **4-9** in solution have been determined by p.m.r. spectroscopy.

INTRODUCTION

In the literature, several reactions of 5-alkyl- and 5-aryl-tetrazoles with electrophilic reagents, leading to the formation of various heterocyclic rings, have been reported[1–5]; the synthesis of oxadiazole derivatives has been widely described. Thus, the reaction of 5-alkyl- and 5-aryl-tetrazoles with acyl chlorides or acid anhydrides afforded the corresponding oxadiazoles in moderate yield[3–5].

We now describe an extension of the above-mentioned reaction using 5-(polyacetoxyalkyl)tetrazoles (**1**) which, on treatment with acetic anhydride or benzoyl chloride, yield 2-methyl- (**2**) or 2-phenyl-5-(polyacetoxyalkyl)-1,3,4-oxadiazole (**3**), respectively.



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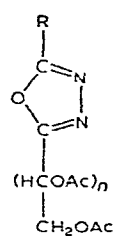
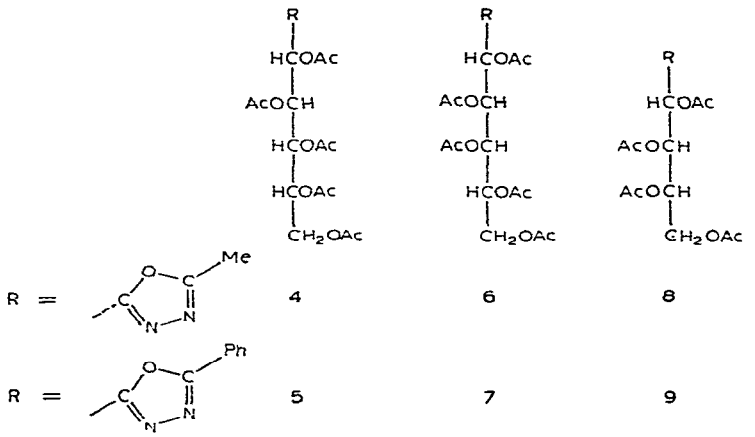


2 R = Me
3 R = Ph

*Dedicated to the memory of Professor Edward J. Bourne.

RESULTS AND DISCUSSION

Reaction of 5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[6] with acetic anhydride afforded 2-methyl-5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-oxadiazole (**4**), and the reaction with benzoyl chloride produced 5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole (**5**). Similar reactions applied to 5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[7] and 5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)tetrazole[6] gave 2-methyl-5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-oxadiazole (**6**), 5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole[8] (**7**), 2-methyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole (**8**), and 2-phenyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole (**9**).



Compounds **4–9** were subjected to mass spectrometry, and their conformations in solution were evaluated by analysis of their respective p.m.r. spectra.

The mass spectra of the phenyloxadiazole derivatives **5**, **7**, and **9** (see Table II) are closely similar to that described by El Khadem *et al.*[8]. In addition to the typical fragmentation of an acetoxyalkyl chain, the spectra show the stability of the oxadiazole nucleus towards electron bombardment, as the major fragment ions are those formed by the cleavage of the acetoxyalkyl chain. This view is confirmed by the strong peaks at *m/e* 218 [2-(acetoxymethyl)-5-phenyloxadiazole], 176 [2-(hydroxymethyl)-5-phenyloxadiazole], and 145 (2-phenyloxadiazole ion)[9]. A γ-fission is reflected by the presence of ions at *m/e* 289, 247, and 205. The important peaks at lower mass are *m/e* 105 (PhCO), 77 (Ph), and 43 (Ac).

For the methyloxadiazole derivatives **4**, **6**, and **8** (Table I), the mass spectra, as expected, resemble those of the phenyl analogues. The main peaks are those formed by an assumed β-cleavage of the acetoxyalkyl chain. Thus, ions at *m/e* 156 [2-(acetoxymethyl)-5-methyloxadiazole], 114 [2-(hydroxymethyl)-5-methyloxadiazole], and 85 (protonated oxadiazole ion) are abundant. It is not possible to assert whether a McLafferty rearrangement, rather than a simple β-cleavage, gives rise to

TABLE I

MAJOR FRAGMENTS RESULTING FROM ELECTRON-IMPACT IONIZATION OF COMPOUNDS 4, 6, AND 8

m/e	*Intensity* (%)[a]			*Assignments*[b]
	4	6	8	
444	<1	<1	—	M
402	<1	<1	—	$M-C_2H_2O$
384	<1	<1	—	M−AcOH
372	—	—	<1	M
359	<1	<1	—	$M-C_2H_2O-Ac$
342	9.7	16.7	—	$M-C_2H_2O-AcOH$
330	—	—	<1	$M-C_2H_2O$
312	—	—	<1	M−AcOH
287	—	—	<1	$M-C_2H_2O-Ac$
282	13.9	16.7	—	$M-C_2H_2O-2AcOH$
270	—	—	21.0	$M-C_2H_2O-AcOH$
257	13.9	8.2	10.0	$(CH_3C_2N_2OCHOAcCHOAcCHOH)^+$
240	6.9	6.1	—	$M-2(C_2H_2O)-2AcOH$
227	2.6	2.1	5.0	$(CH_3C_2N_2OCHOAcCHOAc)^+$
223	5.5	4.1	—	$M-C_2H_2O-2AcOH-AcO$
210	—	—	31.6	$M-C_2H_2O-2AcOH$
198	25.0	20.8	15.8	$(CH_3C_2N_2OC_5H_7O_3)^+$
197	6.0	7.0	3.0	$(CH_3C_2N_2OC_5H_6O_3)^+$
187	20.0	20.0	2.0	$(CH_3C_2N_2HOCHOAcCH_2OH)^+$
185	10.0	8.3	15.8	$(CH_3C_2N_2OCHOAcCHOH)^+$
168	—	—	39.5	$M-2AcOH-2(C_2H_2O)$
156	77.8	75.0	94.7	$(CH_3C_2N_2OCH_2OAc)^+$
151	—	—	13.0	$M-C_2H_2O-2AcOH-AcO$
145	4.0	4.0	4.0	$(CH_3C_2N_2HOCHOHCH_2OH)^+$
143	4.0	4.0	8.0	$(CH_3C_2N_2OCHOHCHOH)^+$
127	19.4	16.7	18.4	$(CH_3C_2N_2OC_2H_4O)^+$
114	58.3	50.0	94.7	$(CH_3C_2N_2OCH_2OH)^+$
85	16.7	10.4	7.9	$(CH_3C_2N_2H_2O)^+$
60	<1	<1	—	AcOH
43	100.0	100.0	100.0	Ac

[a]Expressed as percent of the base peak. [b]Assignments are assumed.

those major peaks. It is also noticeable that a γ-cleavage is operative with formation of ions at *m/e* 227, 185, 143, and the protonated species at *m/e* 187 and 145. The spectra also show the characteristic ions of a polyacetoxyalkyl chain with losses of AcOH, AcO, and Ac fragments.

The p.m.r. spectra of **4–9** in solution in deuteriochloroform show essentially the same pattern of signals as that described for 5-(polyacetoxyalkyl)tetrazoles[10], except for the additional signals from the methyl or the phenyl group attached to the heterocyclic ring. All the spectra, except those corresponding to D-*galacto* derivatives **6** and **7**, were amenable to full analysis at 60 MHz. For **6** and **7**, the signals for H-3 and H-4 overlapped at 60 MHz and even at 100 MHz the spectra provided insufficient data for analysis. However, at 220 MHz, the multiplets could be treated as an ABMX

TABLE II

MAJOR FRAGMENTS RESULTING FROM ELECTRON-IMPACT IONIZATION OF COMPOUNDS 5, 7, AND 9.

m/e	*Intensity* (%)[a]			*Assignments*[b]
	5	7	9	
506	2.5	<1	—	M
464	2.5	<1	—	$M-C_2H_2O$
446	5.1	2.8	—	M−AcOH
434	—	—	2.0	M
421	4.0	<1	—	$M-C_2H_2O-Ac$
404	61.5	31.8	—	$M-C_2H_2O-AcOH$
392	—	—	2.0	$M-C_2H_2O$
374	—	—	9.0	M−AcOH
349	—	—	4.5	$M-C_2H_2O-Ac$
344	66.7	66.7	—	$M-C_2H_2O-2AcOH$
332	—	—	72.7	$M-C_2H_2O-AcOH$
302	30.8	18.2	—	$M-2(C_2H_2O)-2AcOH$
289	9.0	3.0	9.0	$(PhC_2N_2OCHOAcCHOAc)^+$
285	15.0	6.0	—	$M-C_2H_2O-2AcOH-AcO$
272	—	—	100.0	$M-C_2H_2O-2AcOH$
260	25.6	13.6	8.0	$(PhC_2N_2OC_5H_7O_3)^+$
259	43.6	31.8	13.6	$(PhC_2N_2OC_5H_6O_3)^+$
247	12.0	5.0	9.0	$(PhC_2N_2OCHOAcCHOH)^+$
230	—	—	40.9	$M-2(C_2H_2O)-2AcOH$
218	92.3	40.9	50.0	$(PhC_2N_2OCH_2OAc)^+$
213	—	—	36.4	$M-C_2H_2O-2AcOH-AcO$
205	4.0	3.0	5.0	$(PhC_2N_2OCHOHCHOH)^+$
189	23.0	13.6	18.2	$(PhC_2N_2OC_2H_4O)^+$
176	100.0	54.5	95.5	$(PhC_2N_2OCH_2OH)^+$
147	12.8	9.0	9.0	$(PhC_2N_2H_2O)^+$
145	12.8	4.5	4.5	$(PhC_2N_2O)^+$
105	53.8	31.8	36.4	PhCO
77	15.4	13.6	18.2	Ph
60	2.6	2.3	—	AcOH
43	97.4	100.0	86.4	Ac

[a]Expressed as percent of the base peak. [b]Assignments are assumed.

system (where H-2 is M, and H-5 is X) to obtain J_{AB}, J_{AM}, and J_{BX}. The experimental spectra fit perfectly, on the assumption that the H-3 quartet is at lower field than that for H-4. The data on chemical shifts and coupling constants for the above-mentioned compounds are recorded in Table III. From the values of the coupling constants, it was possible to infer the most-probable conformation for each of these compounds in solution.

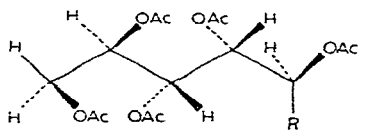
The favoured conformation of 2-methyl-5-(D-*gluco*-1,2,3,4,5-penta-acetoxy-pentyl)-1,3,4-oxadiazole (4) is formed by distortion of the planar, zig-zag conformation by rotation about the C-2–C-3 bond, thus explaining the value of $J_{2,3}$ (7.0 Hz) which indicates an essentially antiparallel disposition of H-2 and H-3. The value of $J_{3,4}$ (3.0 Hz) indicates a gauche arrangement between H-3 and H-4, and that of

TABLE III

VALUES OF CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (J) OF 2-METHYL- AND 2-PHENYL-5-(POLYACETOXYALKYL)-1,3,4-OXADIAZOLES

Compound	*Chemical shift*							*Coupling constant*							
	H-2	*H-3*	*H-4*	*H-5*	*H-5'*	*H-6*	*H-6'*	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
4	6.10	5.80	5.40	5.13	—	4.13	4.18	7.0	3.0	8.0	—	—	3.0	4.5	12.0
5	6.21	5.85	5.51	5.13	—	4.13	4.20	7.0	3.0	8.0	—	—	2.5	4.0	12.0
6	6.02	5.54	5.45	5.36	—	4.06	4.09	2.0	10.0	1.5	—	—	5.0	7.0	12.0
7	6.18	6.09	6.05	5.38	—	4.09	4.11	1.5	10.0	2.0	—	—	5.0	7.0	11.5
8	6.21	5.63	5.28	4.23	4.26	—	—	3.0	8.0	3.0	4.0	12.0	—	—	—
9	6.31	5.70	5.30	4.23	4.26	—	—	3.0	8.5	3.0	5.0	12.0	—	—	—

$J_{4,5}$ (8.0 Hz) indicates H-4 and H-5 to be antiparallel. Hence, the most-probable rotamer for this compound is **10**, in which the orientation about the C-5–C-6 bond is devoid of destabilization factors.



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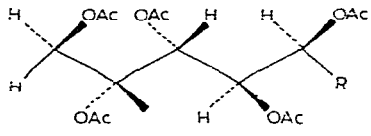

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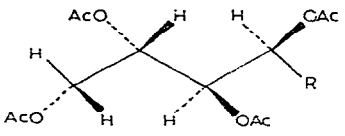

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Likewise, the coupling constants $J_{2,3}$ 7, $J_{3,4}$ 3, and $J_{4,5}$ 8 Hz indicate that 5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole (**5**) also adopts conformation **10**.

The values of the coupling constants for 2-methyl-5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-oxadiazole (**6**) indicate a planar, zig-zag arrangement of the carbon skeleton. The coupling for antiparallel protons, ($J_{3,4}$ 10.0 Hz) and gauche protons ($J_{2,3}$ 2.0, $J_{4,5}$ 1.5 Hz) are consistent with the conformation **11**. Likewise, the coupling constants $J_{2,3}$ 1.5, $J_{3,4}$ 10.0, and $J_{4,5}$ 2.0 Hz for 5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole (**7**) are also indicative of conformation **11**.

The value of 3.0 Hz for $J_{2,3}$ for 2-methyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxy-butyl)-1,3,4-oxadiazole (**8**) indicates that H-2 and H-3 are gauche, whereas the value (8.0 Hz) of $J_{3,4}$ shows H-3 and H-4 to be antiparallel. These values are consistent with the planar, zig-zag conformation **12**. The values of $J_{4,5}$ (3.0 Hz) and $J_{4,5'}$ (4.0 Hz) indicate a preponderance of that rotamer in which both H-5 and H-5′ are almost gauche to H-4, as other arrangements would introduce destabilization by 1,3-interaction of polar groups. Likewise, the coupling constants $J_{2,3}$ 3 and $J_{3,4}$ 8.5 Hz for 2-phenyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole (**9**) are consistent with conformation **12**.

EXPERIMENTAL

General. — T.l.c. was performed on silica gel G (Merck) with 19:1 chloroform–methanol and detection with iodine vapour. Melting points are uncorrected. Optical rotations were determined at 20°.

Mass spectra were recorded with a Varian-Mat CH-7 spectrometer, at an ionizing potential of 70 eV; the temperature of the direct-insertion probe was 100–

110°. U.v. spectra were determined with a Beckman DK2-A spectrophotometer for ethanolic solutions. P.m.r. spectra were recorded with Varian A-60, XL-100, and 220-MHz spectrometers on ~10% solutions in $CDCl_3$ containing 1% of Me_4Si as internal reference. Chemical shifts are given on the δ scale. Coupling constants (Hz) are apparent values, but they serve to differentiate between antiparallel and gauche orientations.

Solvents were removed under diminished pressure below 50°.

2-Methyl-5-(polyacetoxyalkyl)-1,3,4-oxadiazoles. — A solution of each 5-(polyacetoxyalkyl)tetrazole (1 g) in acetic anhydride (2 ml) was heated under reflux until the starting material disappeared (1 h, t.l.c.). The solvent was removed and the residue was treated with water (5 ml). The solid was collected, washed with water, dried, and crystallized from the appropriate solvent. The following compounds were prepared by the above procedure.

2-Methyl-5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-oxadiazole (**4**, 60.7%) [prepared from 5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[6]] had m.p. 155–157° (from methanol), $[\alpha]_D$ +68° (*c* 0.9, chloroform).

Anal. Calc. for $C_{18}H_{24}N_2O_{11}$: C, 48.64; H, 5.40; N, 6.30. Found: C, 48.37; H, 5.36; N, 6.44.

2-Methyl-5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)-1,3,4-oxadiazole (**6**, 62.4%), [prepared from 5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[7]], had m.p. 150–152° [from methanol–water (1:1)], $[\alpha]_D$ +39.5° (*c* 0.8, chloroform).

Anal. Calc. for $C_{18}H_{24}N_2O_{11}$: C, 48.64; H, 5.40; N, 6.30. Found: C, 48.53; H, 5.33; N, 6.35.

2-Methyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole (**8**, 75%), [prepared from 5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)tetrazole[6]], had m.p. 91–93° [from methanol–water (1:1)], $[\alpha]_D$ −4° (*c* 2.9, chloroform).

Anal. Calc. for $C_{15}H_{20}N_2O_9$: C, 48.38; H, 5.37; N, 7.52. Found: C, 48.63; H, 5.66; N, 7.55.

2-Phenyl-5-(polyacetoxyalkyl)-1,3,4-oxadiazoles. — A solution of each 5-(polyacetoxyalkyl)tetrazole (1 g) in anhydrous pyridine (8 ml) was treated with benzoyl chloride (1.5 ml) at 100° until the starting material disappeared (~1 h, t.l.c.). The solution was cooled, a few drops of water were added, and the mixture was poured into ice-water. The insoluble product was treated as individually described. The following compounds were thus prepared.

5-(D-*gluco*-1,2,3,4,5-Penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole (**5**) [prepared from 5-(D-*gluco*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[6]] was a syrup. A solution in methanol was decolourized by several treatments with charcoal and then concentrated to give **5** (64.6%), which was homogeneous by t.l.c. and had $[\alpha]_D$ +49° (*c* 2.6, chloroform), λ_{max} 249 nm (log ε 4.15).

Anal. Calc. for $C_{23}H_{26}N_2O_{11}$: C, 54.54; H, 5.13; N, 5.53. Found: C, 54.79; H, 5.28; N, 5.55.

5-(D-*galacto*-1,2,3,4,5-Penta-acetoxypentyl)-2-phenyl-1,3,4-oxadiazole (**7**, 52%) [prepared from 5-(D-*galacto*-1,2,3,4,5-penta-acetoxypentyl)tetrazole[7]] had m.p. 81–

82° (from ethanol), $[\alpha]_D$ +54° (*c* 0.8, 96% ethanol), λ_{max} 250 nm (log ε 4.42); lit.[8] m.p. 82°, $[\alpha]_D$ +53.9° (*c* 1, ethanol).

2-Phenyl-5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole (9, 56%) [prepared from 5-(L-*arabino*-1,2,3,4-tetra-acetoxybutyl)tetrazole[6]] had m.p. 98–100° (from methanol), $[\alpha]_D$ +13° (*c* 1.1, chloroform), λ_{max} 251 nm (log ε 4.42).

Anal. Calc. for $C_{20}H_{22}N_2O_9$: C, 55.29; H, 5.06; N, 6.45. Found: C, 55.46; H, 5.09; N, 6.71.

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