Carbohydrate Research, 73 (1979) 103–111

C-(POLYACETOXY)ALKYLOXADIAZOLINES AND RELATED COMPOUNDS*

MOHAMED M. ABDEL RAHMAN, EL SAYED H. EL ASHRY, ABDALLAH A. ABDALLAH, AND NAGWA RASHED

Chemistry Department, Faculty of Science, Alexandria University, Alexandria (Egypt)

(Received October 11th, 1978; accepted for publication, November 4th, 1978)

ABSTRACT

The (phenylacetyl)hydrazones of D-galactose, D-glucose, D-mannose, D-arabinose, L-arabinose, D-xylose, and L-sorbose were prepared. The D-galactose and D-arabinose derivatives were converted into their per-*O*-acetylated derivatives (**8** and **9**, respectively). The acyclic structure of **8** was proved from its direct preparation by the condensation of (phenylacetyl)hydrazine with penta-*O*-acetyl-*aldehydo*-D-galactose. Cyclization of 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose (phenylacetyl)hydrazone with boiling acetic anhydride yielded a mixture of two products that could be separated by fractional recrystallization, to give 3-acetyl-5-benzyl-2-(polyacetoxy)alkyl-1,3,4-oxadiazolines; a mechanism for the reaction was proposed The n.m.r. and mass spectra of some of these derivatives were discussed.

INTRODUCTION

This article describes the synthesis and reactions of the (phenylacetyl)hydrazones of some saccharides as a continuation of our work on hydrazine derivatives. 1,3,4-Oxadiazoles and oxadiazolines are of great practical significance, as shown by the growing patent literature on them[2]. They have been thoroughly investigated[2–7] as fungicidal and bactericidal agents, and some of them have analgetic, antipyretic, antiphlogistic, antituberculitic, anticonvulsive, paralytic, hypnotic, and sedative properties. In addition to their biological interest, they have been widely used in various aspects[2], such as in the production of polymers and the preparation of dyes, as light-screening agents in photography, and as scintillators.

Although such heterocyclic derivatives have been extensively studied[2], those having sugar moieties have only recently been prepared[8–12], and, owing to their significance, as well as our interest in the synthesis of heterocyclic derivatives of the carbohydrates[13–19], we have essayed the synthesis of new types of heterocycles from saccharide hydrazones having various sugar moieties and substituents. The synthesis

*Heterocycles from Carbohydrate Precursors. Part XV. For Part XIV, see ref. 1.

of oxadiazoles was achieved either by the oxidative cyclization[8,9] of aroylhydrazones, *e.g.*, of acetates of aldehydo sugar aroylhydrazones to 5-aryl-2-(polyacetoxy)alkyl-1,3,4-oxadiazoles, or by the dehydrative cyclization[10] of 2,3,4,5-tetra-*O*-acetylgalactaric acid bis(aroylhydrazides) with phosphoryl chloride (with triethyl orthoformate[11], these hydrazides give oxadiazoline derivatives). Other approaches to the synthesis of oxadiazoles were the reaction of aldonic acid chlorides with *N*-(benzoylamino)-triphenylphosphinimine[12], and of saccharide tetrazoles[13] with acid anhydrides or acid chlorides. Recently, a preliminary report[14] described the synthesis of oxadiazoline derivatives from D-galactose benzoylhydrazone.

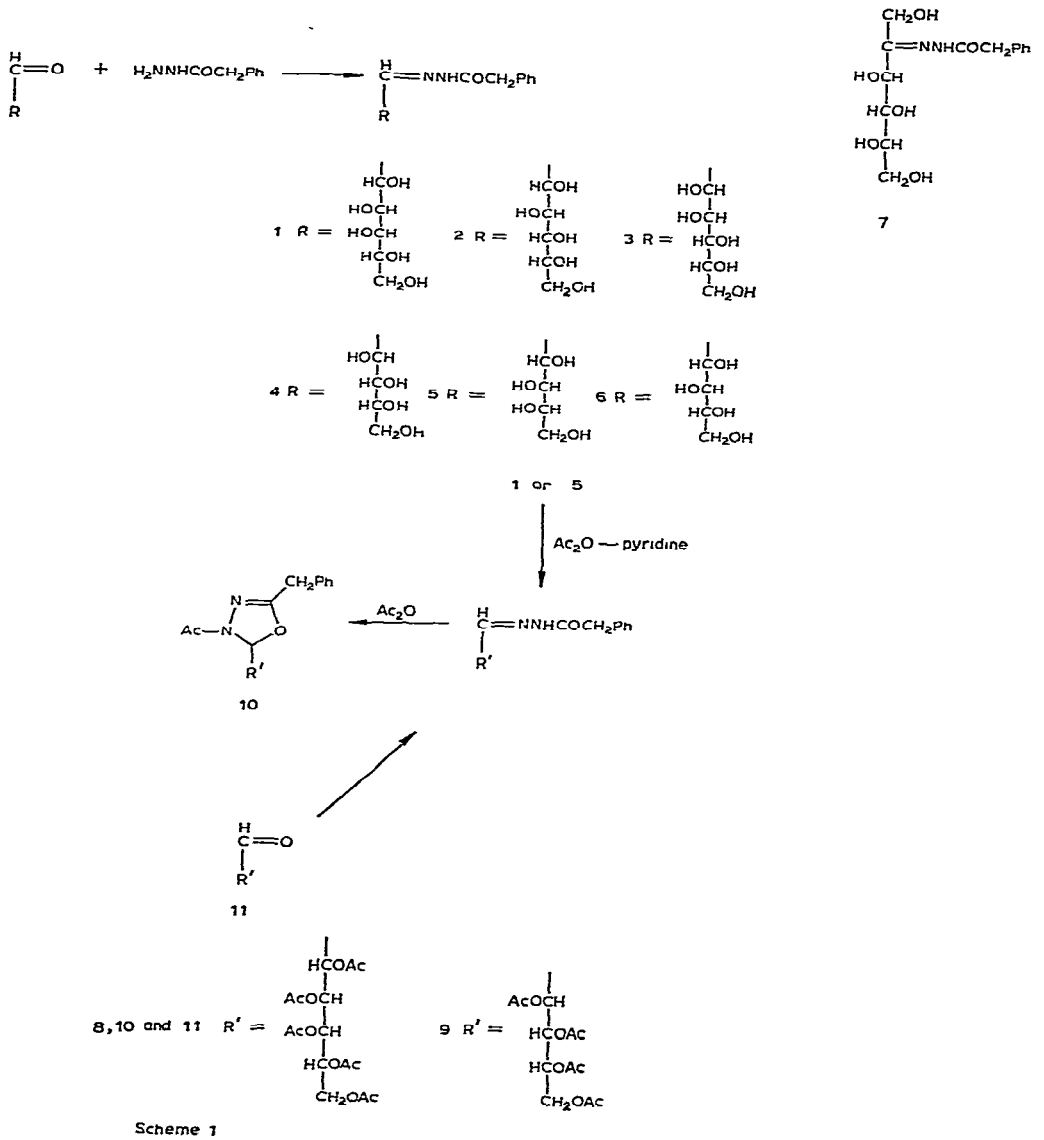
We now describe the cyclization of the (phenylacetyl)hydrazones of aldehydo sugar acetates, in order to explore the reactivity of such types of hydrazones towards cyclizing agents.

RESULTS AND DISCUSSION

Continuing our work on the synthesis and reactions of aroylhydrazones, and our recent interest in the comparative reactivity of (phenylacetyl)hydrazones, it was interesting to ascertain whether saccharide (phenylacetyl)hydrazones behave, towards cyclizing agents, similarly to the acetyl- or the aroyl-hydrazones, where there are some differences[14] between their reaction with acetic anhydride.

Although, the benzoylhydrazones of 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose and 2,3,4,5-tetra-*O*-acetyl-*aldehydo*-D-arabinose are capable of undergoing oxidative cyclization to the corresponding oxadiazoles[8,9], the peracetate of L-rhamnose benzoylhydrazone cannot undergo such cyclization; at first, this behavior was attributed to probably unfavorable geometry[9] of the molecule, but recently, Somogyi[10] considered it to be due to the peracetate's being the 1-*N*-acetyl-2,3,4-tri-*O*-acetyl derivative of L-rhamnopyranosyl 2-benzoylhydrazine. On the other hand, the acetylhydrazones of aldehydo sugar acetates also failed to undergo this reaction, and this behavior was attributed[8] to the diminished enolization of the acetylhydrazone residue compared to that of the aroylhydrazones.

The aldehydo sugar hydrazones needed for this study were prepared by reaction of the selected sugar with (phenylacetyl)hydrazine, whereby the D-galactose, D-glucose, D-mannose, D- and L-arabinose, D-xylose, and L-sorbose (L-*xylo*-2-hexulose) derivatives (**1**–**7**) were prepared. Acetylation of hydrazones **1** and **4** with acetic anhydride in pyridine afforded the corresponding *O*-acetylated derivatives (**8** and **9**) in crystalline form. To confirm the acyclic structure of **8**, an alternative synthesis of it was achieved by the condensation of (phenylacetyl)hydrazine with 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose (**11**), which afforded the same compound (**8**). The infrared (i.r.) spectra of the hydrazones and their acetates showed an absorption band in the carbonyl-frequency region at 1670–1655 cm^{-1} (OCN); in addition, there was a band at 1740 cm^{-1} (OAc) that appeared only in the spectra of the acetyl derivatives. The n.m.r. spectra of hydrazones **1** and **3**–**5** showed the protons on the sugar chain as multiplets at δ 3.8–5.1, 3.7–5.1, 3.8–5.1, and 3.8–5.5, respectively, in



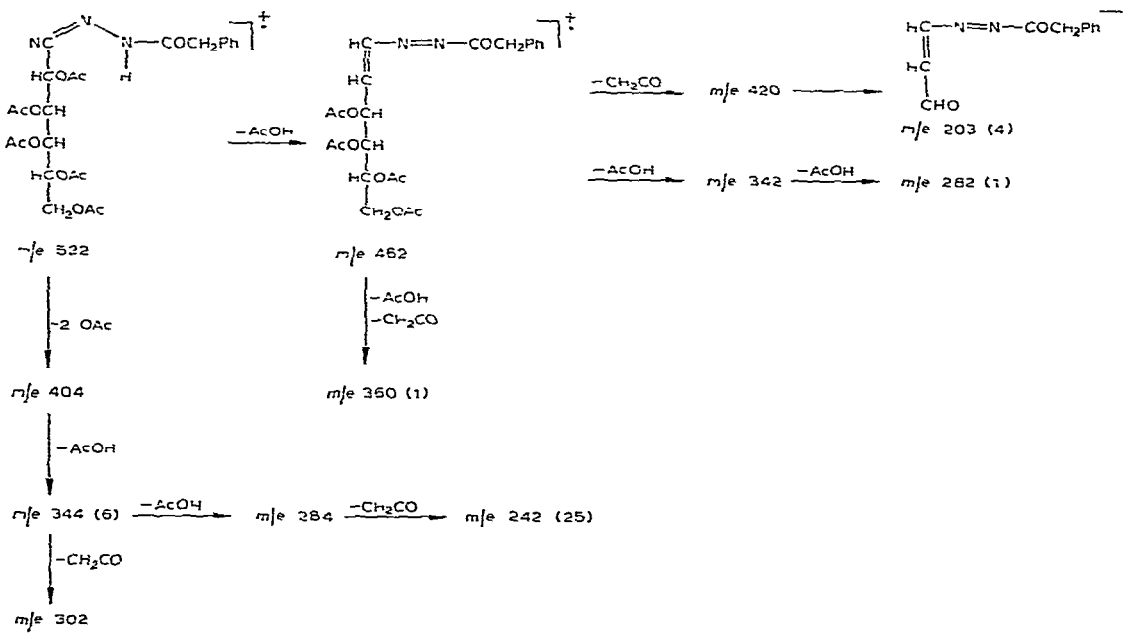
Scheme 1

addition to aromatic protons in the region δ 7.2–7.6 for all of the compounds. The n.m.r. spectrum of acetate **8** showed the five *O*-acetyl groups at δ 1.97, 2.04, 2.12, 2.15, and 2.3. The C-6 methylene protons appeared as two quadruplets, of one-proton intensity each, at δ 3.8 and 4.4, which constitute the AB portion of an ABX system, where the X proton, that on C-5, is buried in the multiplet at δ 5.2–5.7. (A similar nonequivalence of the protons at C-6 was reported[20,21] for the corresponding arylhydrazones, and was attributed to the asymmetry at C-5 and imbalance of the populations of the possible rotamers about the C-5–C-6 bond.) Each of the quadruplets is split by a large, geminal coupling ($J_{6,6'}$ 11.5) and smaller couplings

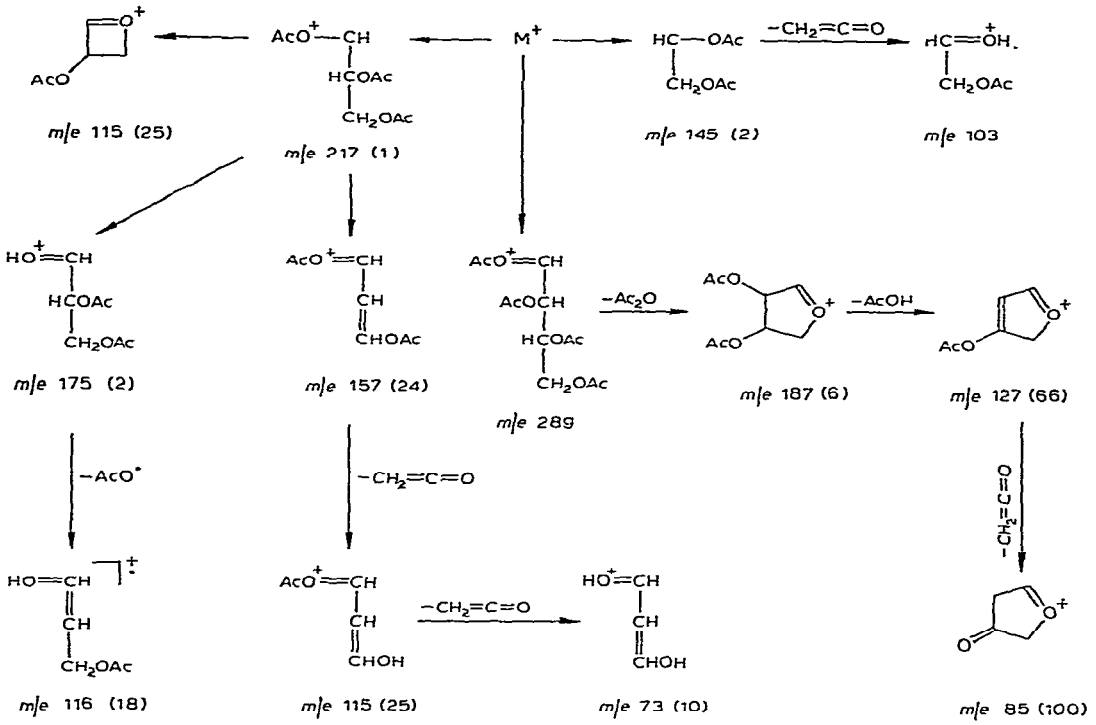
($J_{5,6}$ 5.7 in the first, and $J_{5,6'}$ 7.1 in the second). The rest of the alkyl-chain protons appeared as a multiplet at δ 5.2–5.7, due to H-3, H-4, and H-5, and H-2 appeared at δ 6.2, followed by the phenyl and the C-1 methine protons at δ 7.3–7.9.

Attempted identification, by mass spectrometry, of saccharide hydrazones without derivatization was unsuccessful; however, their peracetates were suitable for this purpose[22]. The stability of the molecular ion of a ketose is sufficiently greater than that of an aldose that it may not appear in the spectrum. In the mass-spectrometric fragmentation of 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose (phenylacetyl)hydrazone (**8**), there is formed a molecular ion peak at *m/e* 522, but its relative abundance is low. The rest of the fragmentation pattern in the spectrum may be divided into two main series of ions, wherein the ions do, or do not, retain the hydrazone residue. Thus, the molecular ion may lose an acetic acid molecule *via* a 1,4-elimination process with the participation of the imino proton, similar to that described for acetates of saccharide hydrazones[22], to give an ion at *m/e* 462 that undergoes a further, successive loss of four more acetic acid molecules, giving ions at *m/e* 342, 282, and 222. Loss of an ·OAc radical and ketene also occurred, as shown in Scheme 2. Rupture of the C-3–C-4 bond, in a similar manner to that observed for other hydrazones, was observed: it occurred here after the loss of ketene to give the ion at *m/e* 203.

The second series of ions is due to rupture of the C-5–C-4, C-4–C-3, and C-3–C-2 bonds, to give the key ions at *m/e* 145, 217, and 289, respectively, the last being the least abundant. Each of these ions loses acetic acid, an acetyl group, ketene, or acetic



Scheme 2



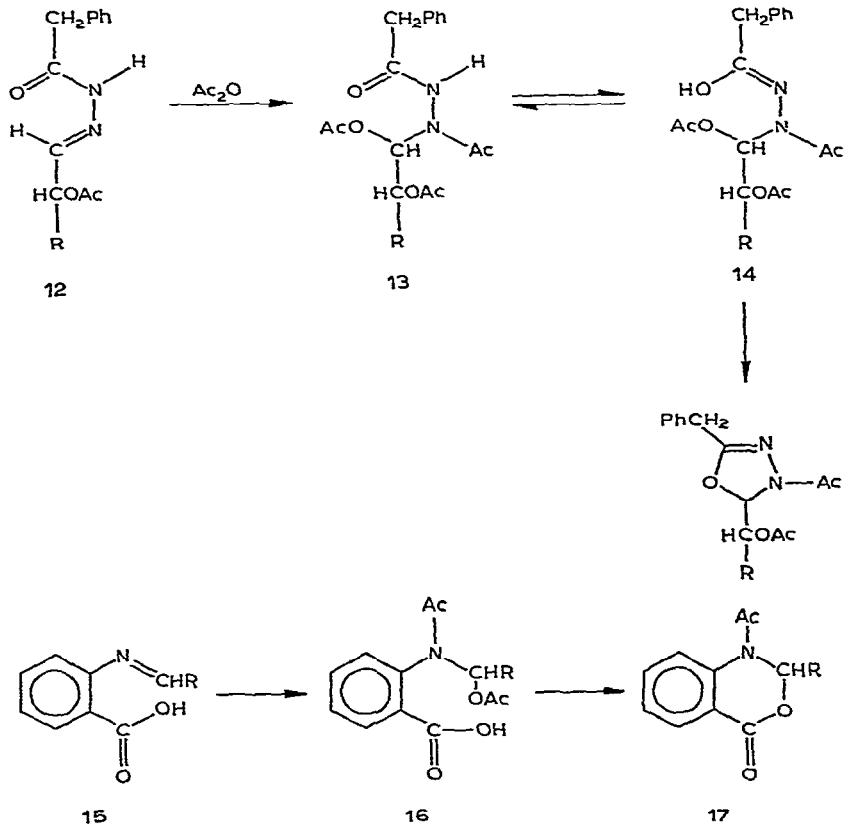
Scheme 3

anhydride, with or without rearrangement, to give the series of ions indicated in Scheme 3. These ions constitute a characteristic pattern for poly(acetoxy)alkyl side-chains[23–27], appearing in the mass spectra of aldononitrile acetates[24,25], alditol acetates[23], and similar compounds[26,27]. The base peak appeared at *m/e* 85. In addition, ions due to the hydrazone residue appeared at *m/e* 161 $(CH{=}N\text{-}NHCOCH_2Ph)^+$ and 91 $(PhCH_2)^+$.

2,3,4,5,6-Penta-*O*-acetyl-*aldehydo*-D-galactose 2-acetylhydrazone was reported[14] to give 3-acetyl-5-methyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoline on reaction with boiling acetic anhydride, whereas, in the presence of pyridine, it gave penta-*O*-acetyl-*aldehydo*-D-galactose N^2,N^2-diacetylhydrazone, previously reported to result from reaction with boiling acetic anhydride[9]. On the other hand, under both sets of conditions, the corresponding benzoylhydrazone afforded 3-acetyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-3-phenyl-1,3,4-oxadiazoline[14]. When 2,3,4,5,6-penta-*O*-*aldehydo*-D-galactose (phenylacetyl)hydrazone (**8**) was boiled with acetic anhydride, it afforded a mixture of two products (as indicated by t.l.c.) that, on repeated recrystallization, gave a pure product (**10**) whose elemental analysis agreed with that calculated for the molecular formula $C_{26}H_{32}N_2O_{12}$. Its i.r. spectrum showed two bands in the carbonyl frequency region at 1740 cm^{-1} (assigned to OAc) and 1675 cm^{-1} [which is shifted to a lower frequency than that of

its corresponding (phenylacetyl)hydrazone (**1**) or its acetate (**8**), by 10 and 5 cm^{-1}, respectively], assigned to N-Ac. Based on similar data, Somogyi[14] assigned the oxadiazoline structure to the products obtained from D-galactose aroylhydrazones. Moreover, there is a report in the literature[28] of similar oxadiazolines being obtained under similar conditions from the aroylhydrazones of simple aldehydes. Consequently, the reaction product **10** was formulated as 3-acetyl-5-benzyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoline. A similar result was obtained when **8** was treated with boiling acetic anhydride–pyridine.

The mechanism of formation of these oxadiazolines probably starts with introduction of the acetic anhydride molecule onto the C=N of the hydrazone residue of **12** (where there are partially positive centers, presumably the carbon atom attacked by the acetate anion, and the acetyl ion that becomes attached to the nitrogen atom) to give the intermediate **13**; this route is similar to that obtaining for the benzalaniline[29] and simple ketone hydrazones[30] on reaction with acetic anhydride. This intermediate **13** then readily loses an acetic acid molecule from its enolized form (**14**). The formation of such an intermediate is also proposed for the action of acetic anhydride on **15** to give **17**, by the loss of acetic acid from **16**.



Scheme 4

Oxidation of penta-*O*-acetyl-*aldehydo*-D-galactose (phenylacetylhydrazone (**8**) is under investigation.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP 200 spectrometer, and n.m.r. spectra (for solutions in pyridine-d_5 or chloroform-*d*), with a Jeol-100 spectrometer, with tetramethylsilane as the standard. Chemical shifts are given on the δ scale. Mass spectra were recorded with an A.E.I. MS 902 instrument; intensities are given in parentheses, as percentages of the base peak. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

TABLE I

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR SUGAR (PHENYLACETYL)HYDRAZONES (**1–7**)

Compound No	*R*	*Yield (%)*	*M.p (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol} *(cm⁻¹)*	
					C	*H*	*N*	*C*	*H*	*N*		
1	D-*galacto*	69	209	$C_{14}H_{20}N_2O_6$	53 8	6 5	8 9	54 2	6.3	8.8	3350	1665
2	D-*gluco*	64	236	$C_{14}H_{20}N_2O_6$	53 8	6 5	8.9	53 9	6 6	9 0	3335	1665
3	D-*manno*	77	198	$C_{14}H_{20}N_2O_6$	53 8	6 5	8 9	54 1	6 4	8 6	3250	1665
4	D-*arabino*	82	200	$C_{13}H_{18}N_2O_5$	55 3	6 4	9 9	55.4	6 5	9 5	3350	1665
5	L-*arabino*	78	203	$C_{13}H_{18}N_2O_5$	55 3	6 4	9 9	55.3	6 2	10 2	3300	1660
6	D-*xylo*	79	235	$C_{13}H_{18}N_2O_5$	55 3	6 4	9 9	55.7	6 1	10 2	3300	1655
7	L-*xylo*	61	233	$C_{14}H_{20}N_2O_6$	53 8	6 5	8 9	53 6	6 5	8.9	3300	1660

TABLE II

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR THE *O*-ACETYL DERIVATIVES **8** AND **9**

Compound No	*R*	*Yield (%)*	*M.p (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{Nujol} *(cm⁻¹)*		
					C	*H*	*N*	*C*	*H*	*N*			
8	D-*galacto*	72	94	$C_{24}H_{30}N_2O_{11}$	55 2	5 8	5.4	55.3	5 8	5 3	3220	1740	1670
9	D-*arabino*	86	83–85	$C_{21}H_{26}N_2O_9$	56 0	5 8	6 2	56 2	5 8	6 0	3225	1740	1660

Sugar (phenylacetyl)hydrazones (**1–7**). — A solution of the monosaccharide (0.01 mol) in water (4 mL) was treated with phenylacetylhydrazine (0.01 mol) in ethanol (6 mL), and the mixture was boiled under reflux for 1 h. The resulting solution was concentrated to ~4 mL and then cooled; the product that separated out was filtered off, washed with alcohol, and dried. Recrystallization was effected from ethanol, giving colorless needles (see Table I).

O-Acetylated derivatives of saccharide (phenylacetyl)hydrazones (**8** *and* **9**). — A solution of compound **1** or **5** (0.2 g) in dry pyridine (15 mL) was treated with acetic anhydride (3 mL), and the mixture was kept overnight at room temperature, and poured onto crushed ice; the product that separated out was filtered off, successively washed with water and sodium hydrogencarbonate solution, dried, and crystallized from ethanol, giving colorless needles (see Table II).

*2,3,4,5,6-Penta-O-acetyl-*aldehydo-D-*galactose (phenylacetyl)hydrazone* (**8**). — A solution of 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose (0.2 g) in ethyl acetate (10 mL) was treated with (phenylacetyl)hydrazine (0.07 g), and the mixture was boiled under reflux for 30 min, concentrated, and cooled. The product that separated was recrystallized from ethanol, giving colorless needles, m.p. 95–97°, identical with that obtained by the acetylation of **1**.

*3-Acetyl-5-benzyl-2-(1,2,3,4,5-penta-*O*-acetyl-*D-galacto-*pentitol-*1*-yl)-1,3,4-oxadiazoline* (**10**). — (*a*) A solution of compound **8** (0.3 g) in acetic anhydride (5 mL) was boiled under reflux for 1 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, successively washed with sodium hydrogencarbonate solution and water, and dried. The product showed two spots in t.l.c., but, upon repeated recrystallization, it gave a pure product, m.p. 110–112°; ν_{max}^{Nujol} 1740 (OAc), 1675 (OCN), and 1630 cm^{-1} (C=N).

Anal. Calc. for $C_{26}H_{32}N_2O_{12}$: C, 55.3; H, 5.7; N, 5.0. Found: C, 55.2; H, 5.5; N, 4.9.

(*b*) A suspension of compound **8** (0.5 g) in a mixture of pyridine (5 mL) and acetic anhydride (5 mL) was heated under reflux on a boiling-water bath for 1.5 h. The mixture was then cooled, and poured onto crushed ice, and the solid that separated out was filtered off, washed with sodium hydrogencarbonate solution, and dried. It was repeatedly recrystallized from ethanol, to give a product identical with that obtained in *a*.

REFERENCES

1 E. S. H. El Ashry, R. Soliman, and K. Mackawy, *Carbohydr. Res*, 72 (1979) 305–308.
2 A. Hetzheim and K. Mockel, *Adv. Heterocycl. Chem*, 7 (1970) 183–224.
3 J. H. Boyer, *Heterocycl. Comp*, 7 (1961) 462–540.
4 W. R. Sherman, U. S Pat., (1962) 3,024,233; *Chem Abstr*, 57 (1962) 11,204.
5 H. Inoue and A. Saikachi, Jpn. Pat., (1963) 20,572; *Chem. Abstr.*, 60 (1964) 2952.
6 H. Saikachi, Br. Pat., (1964) 949,288; *Chem. Abstr*, 60 (1964) 10,692.
7 W. R. Sherman, *J. Org. Chem.*, 26 (1961) 88–95.
8 H. El Khadem, M. A. E. Shaban, E S. H. El Ashry, and M. A. M Nassr, *Abstr Pap. C I.C.–Am. Chem. Soc. Meet*, *Toronto*, (1970) Carb-7; H El Khadem, M. A. E Shaban, and M. A M. Nassr, *Carbohydr. Res.*, 23 (1972) 103–109.
9 M. A. E. Shaban and M. A. M. Nassr, *Org. Prep. Proced. Int.*, 8 (1976) 107–112.
10 L. Somogyi, *Carbohydr. Res.*, 64 (1978) 289–292.
11 M. A. E. Shaban, E. S. H. El Ashry, M. A. M. Nassr, and V. N. Reinhold, *Carbohydr. Res.*, 42 (1975) c1–c3.
12 J. M. J. Tronchet and R. E. Moskalyk, *Helv. Chim. Acta*, 55 (1972) 2816–2819.
13 A. M. Seldes, E. G. Gros, I. M. E. Thiel, and J. O. Deferrari, *Carbohydr Res.*, 49 (1976) 49–56.
14 L. Somogyi, *Carbohydr. Res.*, 54 (1977) c14–c16.

15 E. S. H. EL ASHRY AND Y. EL ASHRY, *Chem. Ind. (London)*, (1976) 372–373.
16 E. S. H. EL ASHRY, Y. EL KILANY, AND F. SINGAB, *Carbohydr Res*, 56 (1977) 93–104.
17 E. S. H. EL ASHRY, M. NASSR, AND F. SINGAB, *Carbohydr. Res.*, 56 (1977) 200–206
18 E. S. H. EL ASHRY, I. E. EL KHOLY, AND Y. EL KILANY, *Carbohydr. Res.*, 59 (1978) 417–426; 60 (1978) 303–314, 393–399.
19 E. S. H. EL ASHRY, M. M. A. ABDEL RAHMAN, S MANCY, AND Z M EL SHAFEI, *Acta Chim. Acad. Sci. Hung*, 95 (1977) 409–415
20 M. L WOLFROM, G. FRAENKEL, D. R. LINEBACK, AND F. KOMITSKY, JR, *J Org. Chem.*, 29 (1964) 457–461.
21 P. M. NAIR AND J D ROBERTS, *J. Am. Chem Soc*, 79 (1957) 4565–4566.
22 V. KOVÁČIK, K. LINEK, AND R. SANDTNEROVÁ, *Carbohydr. Res*, 38 (1974) 300–304.
23 L. S. GOLOVKINA, O. S. CHIZHOV, AND N. S WULFSON, *Izv Akad Nauk SSSR, Ser. Khim*, (1966) 1915–1926
24 B. A DMITRIEV, L. V. BACKINOWSKY, O. S CHIZHOV, B M. ZOLOTAREV, AND N. K. KOCHETKOV, *Carbohydr. Res*, 19 (1971) 432–435.
25 J. SZAFRANEK, C. D. PFAFFENBERGER, AND E. C. HORNING, *Carbohyar. Res*, 38 (1974) 97–105.
26 S. HANESSIAN, *Methods Biochem. Anal*, 19 (1970) 105–228
27 N. K. KOCHETKOV AND O. S. CHIZHOV, *Adv Carbohydr. Chem.*, 21 (1966) 39–93
28 R. S. SAGITULLIN AND A. N. KOST, *Vestn Mosk. Univ. Ser. Mat. Mekh. Astron. Fiz. Khim.*, 14 (1959) 187–193; *Chem. Abstr.*, 54 (1960) 17,383*h*.
29 J. B. EKELEY, M. C SWISHER, AND C C JOHNSON, *Gazz Chim. Ital*, 62 (1932) 81–84.
30 H. L. YALE, K. LOSEE, J. MARTINS, H. HOISING, F. M. PERRY, AND J. BERNSTEIN, *J Am Chem Soc.*, 75 (1953) 1933–1942.