Carbohydrate Research, 113 (1983) 273–279
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SACCHARIDE (2,4-DICHLOROPHENOXY)ACETYLHYDRAZONES, THE MECHANISM OF HETEROCYCLIZATION UNDER ACETYLATIVE CONDITIONS*

EL SAYED H. EL ASHRY**, YELDEZ EL KILANY, ABDALLAH A. ABDALLAH, AND KAMEL MACKAWY
Chemistry Department, Faculty of Science, Alexandria University, Alexandria (Egypt)

(Received August 24th, 1982; accepted for publication, September 21st, 1982)

ABSTRACT

The synthesis of the (2,4-dichlorophenoxy)acetylhydrazones of a number of monosaccharides is described. The reaction of the corresponding D-galactose derivative with acetic anhydride in pyridine was investigated. Penta-*O*-acetyl-*aldehydo*-D-galactose (2,4-dichlorophenoxy)acetylhydrazone was prepared by reaction of the hydrazine with penta-*O*-acetyl-*aldehydo*-D-galactose, and its ^{1}H-n.m.r. spectrum indicated its existence as two geometric isomers. Reaction of the pentaacetate with boiling acetic anhydride caused its acetylative heterocyclization into 3-acetyl-5-[(2,4-dichlorophenoxy)methylene]-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoline. A generalized mechanism for the heterocyclization, based on "soft" and "hard" acids and bases, is discussed. D-*arabino*-Hexos-2-ulose 2-(2,4-dichlorophenoxy)acetylhydrazone 1-phenylhydrazone was also prepared.

INTRODUCTION

(2,4-Dichlorophenoxy)acetic acid (2,4-D) is effective in inducing calluses from differentiated tissues and organs of plants[3–5] (differentiation). It is also used as a post-emergence, selective herbicide[6,7] to control terrestrial and aquatic broad-leaved weeds in corn, flax, lawns, rice, small grains, and sorghum, and to control brush and weeds in pastures. The acid is usually formulated and marketed as salts or esters. Of the wide variety of such salts and esters that have been tested[8,9], the isopropyl ester is the most popular for emulsion formulation. However, its indiscriminate use led to damage to crops neighboring those sprayed, and, because the isopropyl ester is somewhat volatile, the less-volatile poly(propylene glycol) esters have been used[5] to lessen this drift hazard. Consequently, the formulation of 2,4-D as hydrazones should be interesting.

Continuing our work on the attachment of biologically important molecules

---

*Heterocycles from Carbohydrate Precursors, Part XXIV. For Part XXIII, see ref. 1. The Scope of the Reactions of Hydrazines and Hydrazones, Part XIV. For Part XIII, see ref. 2.

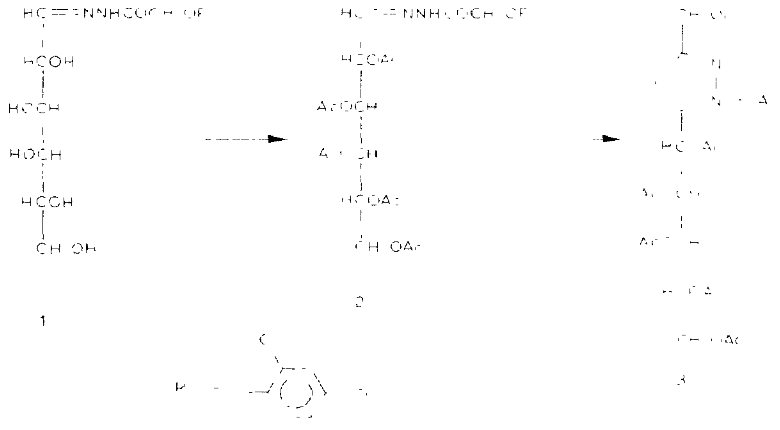
**To whom enquiries should be addressed.

0008-6215/83/0000–0000/$ 03.00, © 1983 — Elsevier Scientific Publishing Company

to carbohydrate derivatives, the attachment of sulfa drugs[10,11], *p*-acetamidobenzoic acid[12], and phenoxyacetic acid[13] has been achieved. In the present work, (2,4-dichlorophenoxy)acetic acid hydrazide was attached to some monosaccharides, and its reactivity compared with those of other types of hydrazones is discussed.

RESULTS AND DISCUSSION

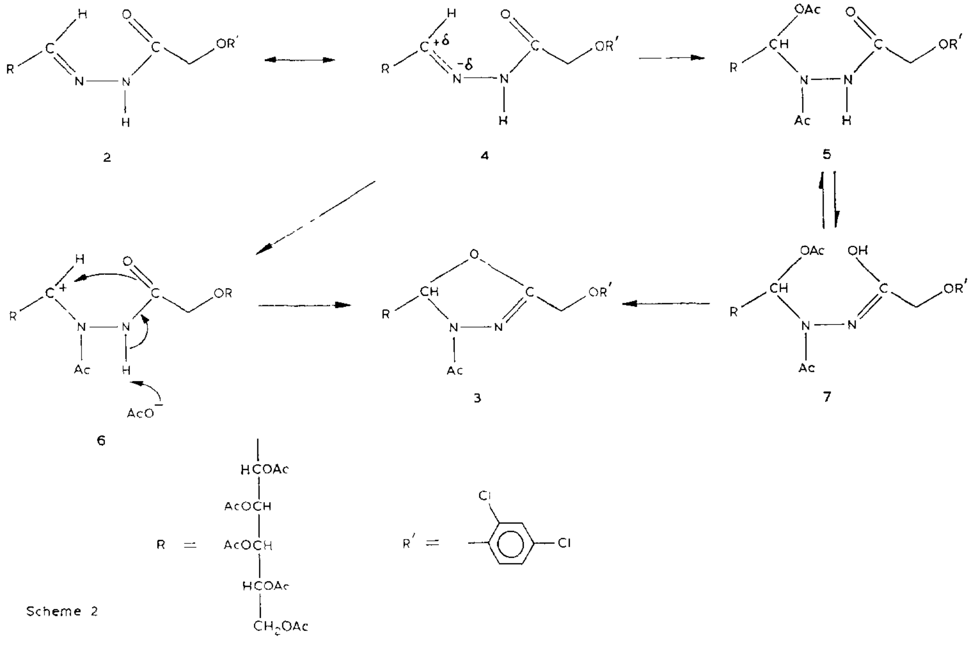
Reaction of (2,4-dichlorophenoxy)acetylhydrazine with D-galactose afforded the corresponding hydrazone (**1**), whose infrared (i.r.) spectrum showed the band for the OCN group at 1675 cm^{-1}. Acetylation of D-galactose (2,4-dichlorophenoxy)acetylhydrazone (**1**) with acetic anhydride in pyridine afforded a crystalline product, t.l.c. of which showed the presence of two compounds, tentatively assigned as the anticipated penta-*O*-acetyl derivative and its cyclized product or *N,O*-acetyl derivative (see Scheme 1). Repeated recrystallization of the mixture afforded a single product that was identified as penta-*O*-acetyl-*aldehydo*-D-galactose (2,4-dichlorophenoxy)acetylhydrazone (**2**). Its structure was conclusively confirmed by its unequivocal synthesis by the condensation of (2,4-dichlorophenoxy)acetylhydrazine with penta-*O*-acetyl-*aldehydo*-D-galactose. The latter route indicated the acyclic structure of acetate **2**, in addition to confirming that it was not a heterocyclized product. The i.r. spectrum of **2** showed a band for the acetyl group at 1760 cm^{-1}, in addition to one for the OCN group of the hydrazone group at 1680 cm^{-1}. The mass spectrum of **2** showed a molecular-ion peak agreeing with the proposed structure. The ^{1}H-n.m.r. spectrum of **2** showed signals for five acetyl groups as singlets, at δ 2.02, 2.08, 2.12, and 2.16; the C-6 methylene group appeared as two quartets of one-proton intensity each, at δ 3.9 and 4.3, each split by a large coupling-constant ($J_{6,6'}$ 12 Hz) and a smaller coupling-constant ($J_{5,6}$ 8 Hz in the first quartet and $J_{5,6'}$ 5 Hz in the second), due to the presence of H-5,6,6' in an arrangement that allows the *cis* and *trans*



Scheme 1

relationship of H-6 and H-6′ with H-5, respectively, as a result of the restricted rotation. The signals of H-2, 3, 4, and 5 of the sugar residue appeared at δ 5.5 as a multiplet of four-proton intensity, and the aromatic protons at δ 7.2. The methylene group of the phenoxyacetyl residue appeared as two singlets, at δ 4.60 and 5.46, whose sum of integration was calculated as two protons; however they had different relative intensities, indicating that they belonged to two compounds whose methylene groups are located in different environments. Similarly, the imino proton appeared as two singlets, at δ 9.50 and 10.05, whose ratio was the same as that of the two methylene groups. The ratio was found to vary from one sample to another on repeated recrystallization. Such a pattern in the ^{1}H-n.m.r. spectrum indicated that **2** exists as two geometric isomers. The nature of these geometric isomers will be correlated with the $C=N$ function, which gives the possibility of *syn* and *anti* isomers, as well as with the presence of *ortho* substituents, which may restrict the rotation within the hydrazone residue.

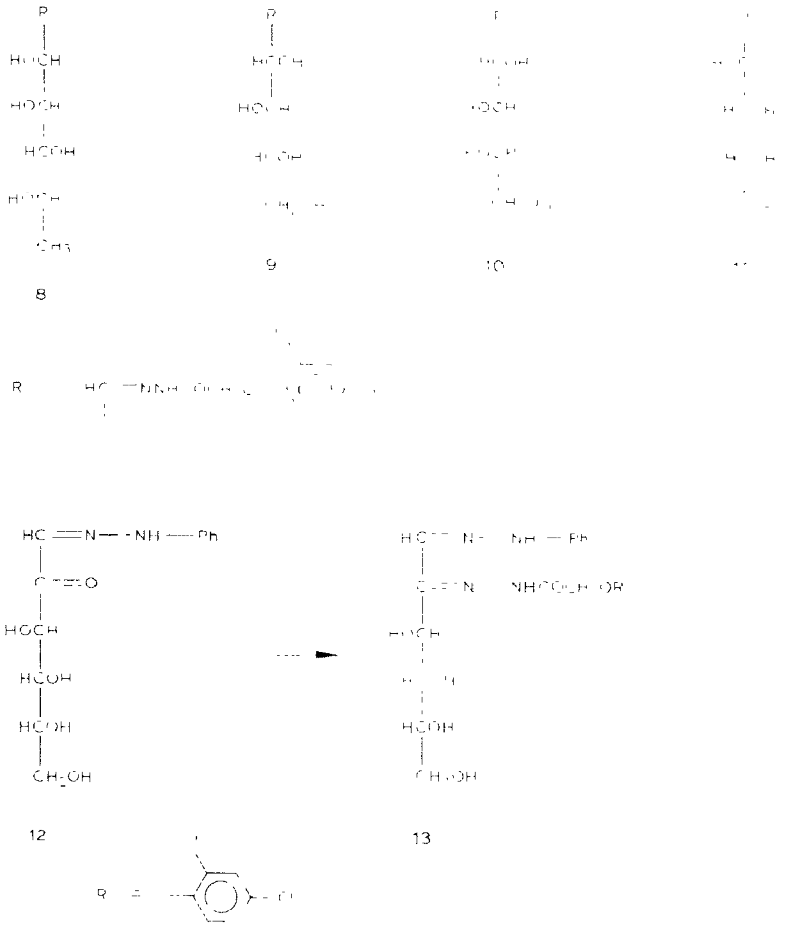
3-Acetyl-5-methyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoline was obtained by the action of boiling acetic anhydride on 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose 2-acetylhydrazone, whereas the action of acetic anhydride in pyridine gave penta-*O*-acetyl-*aldehydo*-D-galactose N^2,N^2-diacetylhydrazone. The action of boiling acetic anhydride on the corresponding benzoylhydrazone, as well as on the (phenylacetyl)hydrazone, afforded the respective oxadiazoline. The mode of action of acetic anhydride on saccharide (aryloxyacetyl)-hydrazones[13] has been studied[14], and we report here that action on (2,4-dichlorophenoxyacetyl)hydrazones. When **2** was boiled with acetic anhydride, a product



Scheme 2

was obtained whose elemental analysis agreed with the molecular formula $C_{26}H_{30}Cl_2N_2O_{13}$. From the mode of preparation, as well as its spectral data, it was formulated as 3-acetyl-[(2,4-dichlorophenoxy)methylene]-2-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-1,3,4-oxadiazoline (**3**). The mechanism of the acetylative heterocyclization of **2** may be depicted as reported earlier[15], by considering the tendency of the C = N to be partially charged, as in **4**, and, consequently, the partially charged carbonium ion will be attacked by the acetate anion, and the acetyl ion will attack the nitrogen atom, to give intermediate **5**, that loses an acetic acid molecule from its enolized form **7**, to give **3**. Alternatively, the mechanism can be explained on the basis of the "hard" and "soft" acid and base principle[16]. The harder acylating reagent reacts with the harder nitrogen atom, rather than with the softer oxygen atom, to give the intermediate **6**, and this acylation favors the cyclization of **6** to **3**.

Reaction of L-rhamnose, D-xylose, D-arabinose, and L-arabinose with (2,4-dichlorophenoxy)acetylhydrazine afforded the corresponding hydrazones **8**–**11**.



Scheme 3

Finally, the reaction of D-*arabino*-hexos-2-ulose 1-phenylhydrazone (**12**)with (2,4-dichlorophenoxy)acetylhydrazine (see Scheme 3) afforded a mixed bis(hydrazone), D-*arabino*-hexos-2-ulose 2-[(2,4-dichlorophenoxy)acetylhydrazone] 1-phenylhydrazone (**13**). Its infrared spectrum showed the band of the OCN group at 1690 cm^{-1}.

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 spectrophotometer, 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. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

D-*Galactose (2,4-dichlorophenoxy)acetylhydrazone* (**1**). — A solution of D-galactose (1.80 g, 0.01 mol) in water (4.0 mL) was treated with (2,4-dichlorophenoxy)-acetylhydrazine (1.76 g, 0.01 mol) in ethanol (60 mL), and the mixture was boiled under reflux for 1 h. The resulting solution was concentrated, and then cooled, and the product that separated out was filtered off, washed with alcohol, and dried. Recrystallization was effected from ethanol, giving colorless needles (yield 70%); m.p. 117–119°; ν_{max}^{KBr} 1675 cm^{-1} (OCN).

Anal. Calc. for $C_{14}H_{18}Cl_2N_2O_7 \cdot H_2O$: C, 40.5; H, 4.9; N, 6.8. Found: C, 40.1; H, 5.3; N, 6.6.

*2,3,4,5,6-Penta-*O*-acetyl-*aldehydo-D-*galactose (2,4-dichlorophenoxyacetyl)hydrazone* (**2**). — (*a*) A solution of compound **1** (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 sodium hydrogencarbonate solution and water, and dried. On repeated recrystallization from ethanol, it afforded colorless needles (yield 40%); 160–161°; ν_{max}^{KBr} 1760 (OAc) and 1680 cm^{-1} (OCN); ^{1}H-n.m.r.-spectral data ($CDCl_3$): δ 2.02, 2.08, 2.12, and 2.16 (4 s, 15 H, 5 Ac), 3.9 (q, 1 H, $J_{5,6'}$ 8, $J_{6,6'}$ 12 Hz, H-6'), 4.3 (q, 1 H, $J_{5,6}$ 5 Hz, H-6), 4.60 and 5.02 (2 s, 2 H, OCH_2O-), 4.5 (m, 4 H, H-2,3,4,5), 7.2 (m, 4 H, H-1 and aromatic protons), and 9.5 and 10.1 (2 s, 1 H, NH).

Anal. Calc. for $C_{24}H_{28}Cl_2N_2O_{12}$: C, 47.5; H, 4.7; N, 4.6. Found: C, 47.2; H, 4.3; N, 4.7.

(*b*) A solution of 2,3,4,5,6-penta-*O*-acetyl-*aldehydo*-D-galactose (0.5 g) in ethanol (20 mL) was treated with the equivalent amount of (2,4-dichlorophenoxy)-acetylhydrazine, and the mixture was heated under reflux for 1 h, concentrated, and cooled. The product that separated out was recrystallized from ethanol, to give colorless needles (65%), identical with the compound obtained by method a.

*3-Acetyl-5-[(2,4-dichlorophenoxy)methylene]-2-(1,2,3,4,5-penta-*O*-acetyl-*D-galacto-*pentitol-1-yl)-1,3,4-oxadiazoline* (**3**). — A solution of compound **2** (0.3 g) in acetic anhydride (5 mL) was boiled under reflux for 1 h. The resulting solution was

TABLE I

MICROANALYTICAL AND INFRARED ABSORPTION DATA FOR SACCHARIDE (2,4-DICHLOROPHENOXY)ACETYLHYDRAZONES

Compound	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found*			ν_{max}^{Nujol} *(cm^{-1})*
				C	*H*	*N*	*C*	*H*	*N*	
8	65	190–191	$C_{14}H_{18}Cl_2N_2O_6$	44.1	4.8	7.4	44.2	4.7	7.4	1685
9	70	176–178	$C_{13}H_{16}Cl_2N_2O_6$	42.6	4.4	7.7	42.5	4.7	4.5	1670
10	75	172–173	$C_{13}H_{16}Cl_2N_2O_6$	42.6	4.4	7.7	42.4	4.3	7.6	1680
11	55	175–176	$C_{13}H_{16}Cl_2N_2O_6$	42.6	4.4	7.7	42.5	4.4	7.7	1655

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 was recrystallized from ethanol (yield 55%): m.p. 207–208°; ν_{max}^{KBr} 1725 (OAc) and 1675 cm^{-1} (OCN).

Anal. Calc. for $C_{26}H_{30}Cl_2N_2O_{13}$: C, 48.1; H, 4.7; N, 4.3. Found: C, 48.5, H, 5.0; N, 4.2.

Saccharide (2,4-dichlorophenoxy)acetylhydrazones (**8–11**). — A solution of the monosaccharide (0.01 mol) in water (4 mL) was treated with (2,6-dichlorophenoxy)-acetylhydrazine (0.01 mol) in ethanol (60 mL), and the mixture was boiled under reflux for 1 h. The resulting solution was concentrated, and then cooled, and the product that separated out was filtered off, washed with alcohol, and dried. Recrystallization was effected from ethanol, giving colorless needles (see Table I).

D-arabino-*Hexulose 2-[(2,4-dichlorophenoxy)acetylhydrazone] 1-(phenylhydrazone)* (**13**). — A solution of compound **12** (0.2 g) in ethanol (20 mL) was treated with a solution of (2,4-dichlorophenoxy)acetylhydrazine (0.2 g) in ethanol, and the mixture was heated for 5 min on a steam bath. On cooling, the product crystallized from the mixture as pale-yellow needles, m.p. 192–193°; ν_{max}^{Nujol} 1690 cm^{-1} (CN).

Anal. Calc. for $C_{20}H_{22}Cl_2N_4O_6$: C, 49.6; H, 4.5; N, 11.6. Found. C, 49.5. H, 4.6; N, 11.4.

REFERENCES

1 E. S. H. EL ASHRY, M. H. NASSR, AND M. SHOUKRY, *Carbohydr. Res.*, 83 (1980) 79–84.
2 E. S. H. EL ASHRY, K. MACKAWY, AND Y. EL KILANY, *Sci. Pharm.*, 48 (1980) 225–228.
3 T. YASUDA AND Y. YAMADA, *FEBS Lett.*, 18 (1971) 115–117.
4 B. KAUL AND E. J. STABA, *Science*, 150 (1965) 1731.
5 J. G. TORREY, J. REINERT, AND N. MERKEL, *Am. J. Bot.*, 49 (1962) 420–425.
6 O. M. ALY AND S. D. FOUST, *J. Agric. Food Chem.*, 12 (1964) 541–546.
7 M. T. SHAFIK, H. C. SULLIVAN, AND H. F. ENOS, *Int. J. Environ. Anal. Chem.*, 1 (1971) 23–33.
8 H. MARTIN, *The Scientific Principles of Crop Protection*, 6th edn., Arnold, London, 1973, pp. 272–275.
9 H. E. THOMSON, C. P. SWANSON, AND A. G. NORMAN, *Bot. Gaz.*, 107 (1946) 476–507.
10 R. SOLIMAN, E. S. H. EL ASHRY, AND M. ABDEL RAHMAN, *Pharmazie*, 34 (1979) 253.

11 R. Soliman, E. S. H. El Ashry, I. E. El Kholy, and Y. El Kilany, *Carbohydr. Res.*, 67 (1978) 179–188.

12 E. S. H. El Ashry, R. Soliman, and K. Mackawy, *Carbohydr. Res.*, 72 (1979) 305–308.

13 E. S. H. El Ashry, K. Mackawy, and Y. El Kilany, unpublished results.

14 K. Mackawy, M.Sc. Thesis, Alexandria University, 1979.

15 M. M. Abdel Rahman, E. S. H. El Ashry, A. A. Abdallah, and N. Rashed, *Carbohydr. Res.*, 73 (1979) 103–111.

16 R. G. Peterson and J. Songstad, *J. Am. Chem. Soc.*, 89 (1967) 1827–1836.