HETEROCYCLES FROM SACCHARIDE HYDRAZONES

PART I. SACCHARIDE 1,3,4-OXADIAZOLES[1,2]

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(Received December 27th, 1971)

ABSTRACT

Oxidation, with iodine–mercuric oxide, of acetylated saccharide aroylhydrazones and of aromatic aldehyde hydrazones yields 5-aryl-2-(polyacetoxyalkyl)-1,3,4-oxadiazoles and 2,5-diaryl-1,3,4-oxadiazoles, respectively. On de-*O*-acetylation, saccharide oxadiazole acetates rearrange to the tautomeric, cyclic iminolactones which, on reacetylation, regenerate the starting oxadiazoles. Attempted dehydration of saccharide acetyl- and benzoyl-hydrazones by treatment with boiling acetic anhydride under reflux resulted in the formation of peracetylated *N*,*N*-diacetylhydrazones and *N*-acetyl-*N*-benzoylhydrazones, respectively.

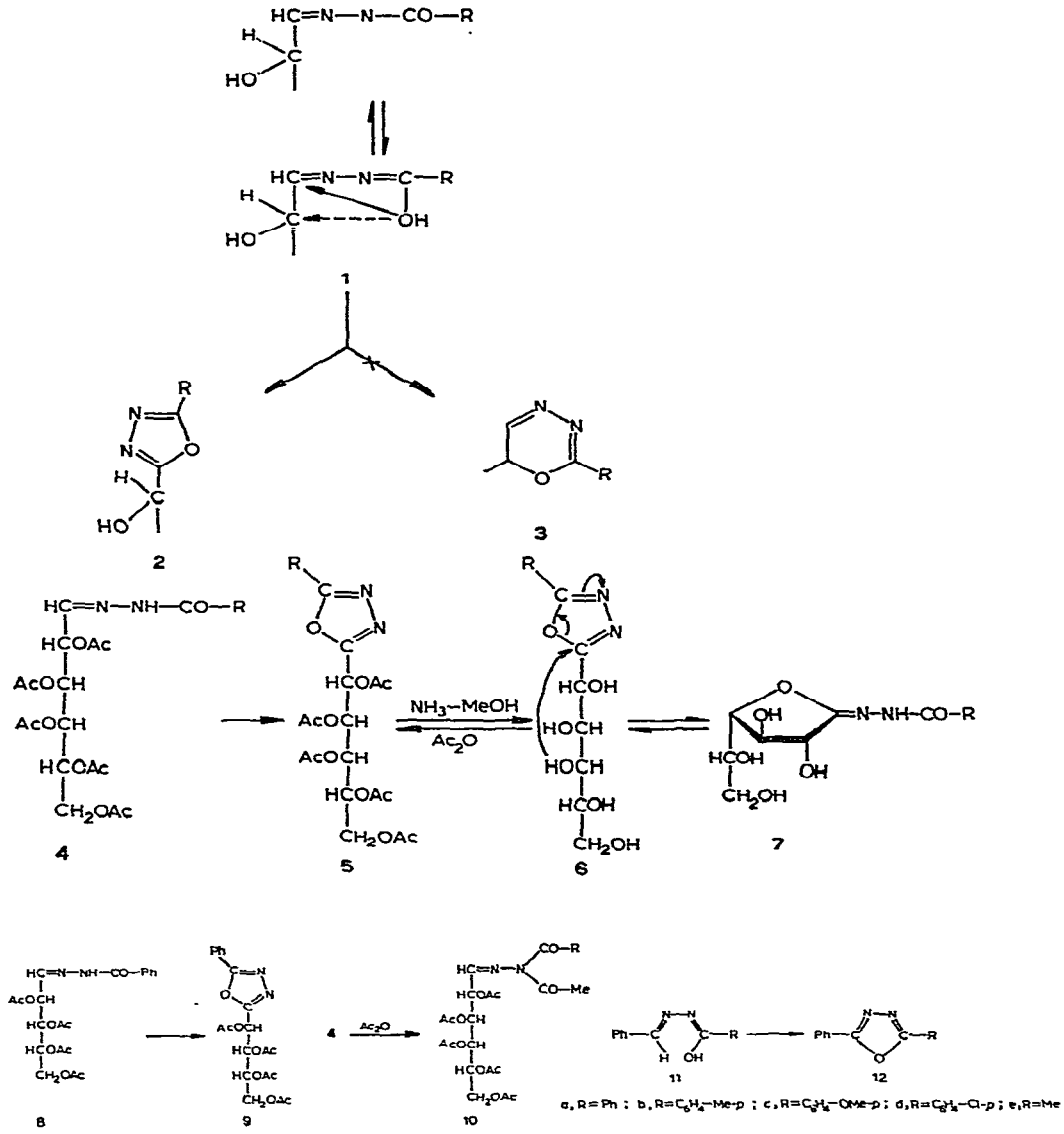
INTRODUCTION

Continuing our work on the synthesis of nitrogen heterocycles from saccharide aroyl- [3–5] and aryl[6–8]-osazones, we have attempted to synthesize such heterocycles by oxidation and by dehydration of sugar hydrazones. Theoretically, such acetylhydrazones as **1** would be expected to undergo cyclization, either by oxidation of the enolic form to give an oxadiazole ring, as in **2**, or by dehydration to form an oxadiazine, as in **3**. To minimize side reactions that might involve hydroxyl groups of the sugar chain, saccharide acetyl- and benzoyl-hydrazones were first converted into the per-*O*-acetyl derivatives, and these were subjected to (*a*) oxidation with iodine and mercuric oxide, and (*b*) attempted removal of acetic acid (known to occur during boiling with acetic anhydride[6–8]). Cyclization took place during the oxidation, affording oxadiazoles, whereas treatment with acetic anhydride resulted in *N*-acetylation.

DISCUSSION

Oxidation of D-galactose benzoyl- and *p*-substituted-benzoyl-hydrazone acetates (**4a**, **4b**, and **4d**) and of D-arabinose benzoylhydrazone (**8a**) with iodine–mercuric oxide yielded the expected oxadiazoles (**5a**, **5b**, **5d**, and **9a**). Thus, when penta-*O*-acetyl-*aldehydo*-D-galactose benzoylhydrazone[9] (**4a**) was treated with iodine–

mercuric oxide, a reagent known[3–5,10] to convert 1,2-bis(aroylhydrazones) into 1,2,3-triazoles, it afforded a crystalline product (**5a**) that had an elementary analysis agreeing with that calculated for a dehydrogenated hydrazone; its infrared (i.r.) spectrum showed only the acetic ester band at 1740 cm^{-1}; the amide band at about 1690 cm^{-1} found in the spectra of both the parent unacetylated and the acetylated hydrazone was absent (see Fig. 1). Acetyl determination[11] revealed the presence of



five *O*-acetyl groups in both the hydrazone acetate and its oxidation product. This result was confirmed by n.m.r. spectroscopy, which revealed signals of five *O*-acetyl

groups at δ 2.02 (2 Ac), 2.05 (Ac), 2.15 (Ac), and 2.20 (Ac), and the ABX systems of the C-6 methylene protons, which appeared as two quadruplets, at δ 3.92, J_{AB} 12 Hz, J_{AX} 7 Hz, and δ 4.35, J_{BX} 5 Hz. The rest of the alkyl-chain protons appeared between δ 5.4 and 6.3, followed by the phenyl protons between δ 7.3 and 8.1 p.p.m. The imino proton of the parent hydrazone acetate (at δ 10.4) was absent. It was thus clear that the pentaacetoxypentyl chain had not been involved in this reaction, and that the dehydrogenation involved only C-1 and the benzoylhydrazone residue attached to it.

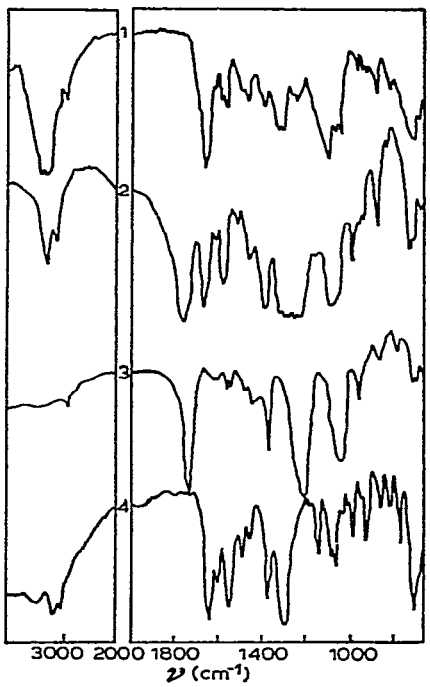


Fig. 1. Infrared spectra of 1, D-galactose benzoylhydrazone; 2, penta-*O*-acetyl-*aldehydo*-D-galactose benzoylhydrazone (**4a**); 3, 2-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazole (**5a**); and 4, D-galactono-1,4-lactone 1-(2-benzoylhydrazone) (**7a**).

The dehydrogenation product was, therefore, assigned structure **5a**, namely, 2-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazole; this was confirmed by mass spectroscopy, which showed (see Fig. 2) typical acetoxyalkyl chain-fragmentation, with successive breakdown at M^+, M−Ac; M−OAc; M−CHOAc, and so on, including major peaks at *m/e* 218 due to 2-(acetoxymethyl)-5-phenyloxadiazole, at 176 due to the 2-(hydroxymethyl) derivative, and at 145 for 2-phenyloxadiazole. Important rearrangement peaks appeared at *m/e* 404 (due to cyclization of the M−(OAc+Ac) fragment to a furanoside derivative) and subsequent loss of Ac and OAc, etc. (which afforded peaks at 360, 344, and 302) and its loss of the heterocycle moiety to give the peak at *m/e* 260. At lower mass, important peaks for Ac, Ph, and Bz were observed at 43, 77, and 105, respectively.

The oxidation of saccharide aroylhydrazone acetates to the corresponding

5-aryl-2-(polyacetoxyalkyl)-1,3,4-oxadiazole was also successfully applied to (*a*) penta-*O*-acetyl-*aldehydo*-D-galactose *p*-toluoyl-[9] (**4b**) and (*p*-chlorobenzoyl)-hydrazone[9] (**4d**), which afforded 2-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-5-*p*-tolyl- (**5b**) and 5-(*p*-chlorophenyl)-1,3,4-oxadiazole (**5d**), respectively, and (*b*) tetra-*O*-acetyl-*aldehydo*-D-arabinose benzoylhydrazone[9] (**8a**), which gave 5-phenyl-2-(D-*arabino*-1,2,3,4-tetraacetoxybutyl)-1,3,4-oxadiazole (**9a**). All of the oxadiazoles prepared gave elemental analyses agreeing with those expected, and showed similar i.r. and u.v. spectra.

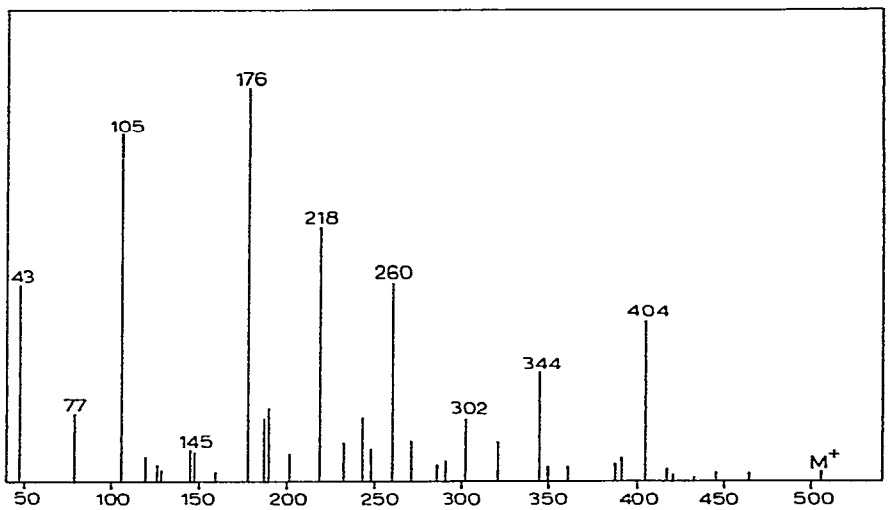


Fig. 2. Mass spectrum of 2-(D-*galacto*-1,2,3,4,5-pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazole (5a).

On the other hand, penta-*O*-acetyl-*aldehydo*-D-galactose acetylhydrazone (**4e**) failed to undergo this reaction, probably because of the diminished enolization of the acetylhydrazone residue compared to that of the aroylhydrazones. This low degree of enolization was also evident from the lack of coloration with ferric chloride (which, with aroylhydrazones, gives the color characteristic of an enol).

Deacetylation of the oxadiazole **5a** with methanolic ammonia at room temperature resulted in the rearrangement of the deacetylated oxadiazole (**6a**) into the imino lactone form (**7a**), which had an elemental analysis agreeing with that calculated, and showed an amide band at 1690 cm^{-1}. Acetylation of **7a** regenerated the parent oxadiazole (**5a**), showing that the imino lactone was in equilibrium with the tautomeric, unacetylated, oxadiazole form **6a**. The n.m.r. spectrum of **7a** showed an imino proton at δ 10.6 p.p.m., and phenyl protons between δ 7.4 and 8.0. The C-2 proton appeared as a doublet at δ 5.75 (J 5 Hz); the C-3, C-4, and C-5 protons appeared as multiplets at δ 4.82, 6.00, and 4.43 p.p.m.; and the methylene protons appeared at δ 3.60 and 4.08, J_{AB} 1 Hz, J_{AX} 3 Hz, J_{BX} 6 Hz. The hydroxyl-group protons appeared between δ 3.1 and 3.4 p.p.m.

The mass spectrum of **7a** did not show a molecular-ion peak, but showed peaks at *m/e* 189 (M−Bz) and 176 (M−BzN), a small rearrangement peak at 145 (due to

the formation of 2-phenyloxadiazole), and Ph, Bz, and $BzNH_2$ peaks at *m/e* 77, 105, and 121.

It was of interest to attempt oxidation, with iodine–mercuric oxide of such nonsugar derivatives as aromatic aldehyde aroylhydrazones. Benzaldehyde benzoylhydrazone (**11a**) and benzaldehyde *p*-toluoylhydrazone (**11b**) yielded the known[12] 2,5-diaryl-1,3,4-oxadiazoles (**12a** and **12b**); benzaldehyde (*p*-methoxybenzoyl)hydrazone (**11c**) and anisaldehyde benzoylhydrazone yielded the same 2-(*p*-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**12c**), and benzaldehyde (*p*-chlorobenzoyl)hydrazone (**11d**) afforded 2-(*p*-chlorophenyl)-5-phenyloxadiazole (**12d**).

Attempted cyclization by elimination of acetic acid from saccharide acylhydrazones by treatment with boiling acetic anhydride proved unsuccessful, and resulted only in *N*-acetylation of the hydrazone group. Thus, penta-*O*-acetyl-*aldehydo*-D-galactose acetylhydrazone (**4e**) gave, with boiling acetic anhydride, penta-*O*-acetyl-*aldehydo*-D-galactose *N,N*-diacetylhydrazone (**10e**), and penta-*O*-acetyl-*aldehydo*-D-galactose benzoylhydrazone (**4a**) yielded penta-*O*-acetyl-*aldehydo*-D-galactose *N*-acetyl-*N*-benzoylhydrazone (**10a**), both having an elemental analysis and i.r. spectral data expected.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler block, and are uncorrected. Infrared spectra were recorded, for potassium bromide discs, with a Unicam SP200 spectrophotometer. N.m.r. spectra and mass spectra were recorded and measured by Mr. M. P. Gilles, Department of Chemistry and Chemical Engineering, Michigan Technological University, on Varian HA100 and M66 instruments, respectively.

2-(D-galacto-1,2,3,4,5-Pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazole (**5a**). — *A. From* **4a**. A suspension of penta-*O*-acetyl-*aldehydo*-D-galactose benzoylhydrazone[9] (**4a**, 1 g) in dry ether (100 ml) was successively treated with yellow mercuric oxide (1.2 g), magnesium oxide (0.2 g), and iodine (0.8 g), and the mixture was stirred for 24 h at room temperature. The suspension was filtered, the inorganic residue was washed with ether, and the filtrate and washings were combined and successively washed with saturated potassium iodide solution, sodium thiosulfate solution, and water, dried (sodium sulfate), and evaporated to a yellowish syrup which crystallized on dissolution in a small volume of dilute methanol. Recrystallization from ethanol–water gave 0.6 g of **5a** as needles, m.p. 82°, $[\alpha]_D$ +53.9° (*c* 1, ethanol); ν_{max}^{KBr} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{23}H_{26}N_2O_{11}$: C, 54.54; H, 5.13; N, 5.53. Found: C, 54.59; H, 5.31; N, 5.23.

B. From **7a**. The deacetylated oxadiazole **7a** (0.5 g) in pyridine (10 ml) was treated with acetic anhydride (10 ml) for 24 h at room temperature. Dilution of the mixture with ice–water gave a product which was filtered off, washed, and dried. Recrystallization from ethanol–water gave 0.4 g of **5a** as needles, m.p. and mixed m.p. 82°; $[\alpha]_D$ +54° (*c* 1, ethanol), having the same i.r. spectrum as that of the compound just described.

Anal. Found: C, 54.81; H, 5.35; N, 5.50.

D-*Galactono-1,4-lactone 1-(2-benzoylhydrazone)* (**7a**). — A solution of compound **5a** (1 g) in methanol (20 ml) was treated with 20% ammonium hydroxide solution (10 ml) for 24 h at room temperature, with occasional shaking. The solution was evaporated *in vacuo*, the residue triturated with a small volume of water, and the suspension filtered. Recrystallization of the solid from ethanol gave 0.3 g of **7a** as needles, m.p. 234°, $[\alpha]_D$ +78° (*c* 1, pyridine); ν_{max}^{KBr} 1650 (CONH) and 3300 cm^{-1} (OH).

Anal. Calc. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.81; 52.80; H, 5.63, 5.57; N, 9.65, 9.41.

2-(D-galacto-*1,2,3,4,5-Pentaacetoxypentyl)-5-p-tolyl-1,3,4-oxadiazole* (**5b**). — A suspension of penta-*O*-acetyl-*aldehydo*-D-galactose *p*-toluoylhydrazone[9] (**4b**, 1 g) in dry ether (100 ml) was treated with yellow mercuric oxide (1.2 g), magnesium oxide (0.2 g), and iodine (0.8 g) for 24 h at room temperature. Processing of the mixture as for the preparation of compound **5a**, and crystallization of the product from ethanol, gave 0.6 g of **5b** as needles, m.p. 130°, ν_{max}^{KBr} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{24}H_{28}N_2O_{11}$: C, 55.38; H, 5.38; N, 5.38. Found: C, 55.41; H, 5.46; N, 5.60.

5-(p-*Chlorophenyl)-2-*(D-galacto-*1,2,3,4,5-pentaacetoxypentyl)-1,3,4-oxadiazole* (**5d**). — Penta-*O*-acetyl-*aldehydo*-D-galactose (*p*-chlorobenzoyl)hydrazone[9] (**4d**, 1 g) was oxidized with iodine–mercuric oxide as described for **5b**, and the product was crystallized from ethanol–water to give 0.7 g of **5d** as needles, m.p. 133°; ν_{max}^{KBr} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{23}H_{25}ClN_2O_{11}$: C, 51.06; H, 4.62; N, 5.18. Found: C, 50.87; H, 4.76; N, 5.15.

5-Phenyl-2-(D-*arabino-1,2,3,4-tetraacetoxybutyl)-1,3,4-oxadiazole* (**9a**). — A suspension of tetra-*O*-acetyl-*aldehydo*-D-arabinose benzoylhydrazone[9] (**8**, 1 g) was oxidized as usual, and the product was crystallized from ethanol–water to give 0.4 g of **9a** as needles, m.p. 105°, $[\alpha]_D$ −15.5° (*c* 1, ethanol); ν_{max}^{KBr} 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{20}H_{22}N_2O_9$: C, 55.29; H, 5.10; N, 6.45. Found: C, 55.25; H, 5.11; N, 6.35.

*Penta-*O-*acetyl-*aldehydo-D-*galactose acetylhydrazone* (**4e**). — A solution of *aldehydo*-D-galactose acetylhydrazone (1 g) was treated with pyridine (10 ml) plus acetic anhydride (12 ml) for 16 h at room temperature. The mixture was then poured into ice–water, and the solid product was filtered off, washed, and dried. Recrystallization from ethanol–water gave 1 g of **4e** as needles, m.p. 190°, ν_{max}^{KBr} 1690 (CONH) and 1735 cm^{-1} (OAc).

Anal. Calc. for $C_{18}H_{26}N_2O_{11}$: C, 48.44; H, 5.87; N, 6.27. Found: C, 48.40; H, 5.5; N, 5.90.

*Penta-*O-*acetyl-*aldehydo-D-*galactose* N,N-*diacetylhydrazone* (**10e**). — A mixture of **4e** (1 g) with acetic anhydride (10 ml) was boiled under reflux for 2 h and then cooled, poured onto crushed ice, and stirred until all of the acetic anhydride had been hydrolyzed. The solid product was filtered off, washed, and dried. Recrystallization

from ethanol–water gave 0.5 g of **10e** as needles, m.p. 256°; ν_{max}^{KBr} 1670 (CON) and 1730 cm^{-1} (OAc).

Anal. Calc. for $C_{20}H_{28}N_2O_{12}$: C, 49.18; H, 5.73; N, 5.73. Found: C, 48.83; H, 5.91; N, 5.84.

*Penta-O-acetyl-*aldehydo-D-*galactose* N-*acetyl*-N-*benzoylhydrazone* (**10a**). — A mixture of penta-*O*-acetyl-*aldehydo*-D-galactose benzoylhydrazone (**4a**, 1 g) and acetic anhydride (10 ml) was boiled for 2 h under reflux and then allowed to cool. Processing of the reaction mixture as previously described gave 0.4 g of **10a** as needles, m.p. 124°; ν_{max}^{KBr} 1680 (CON) and 1740 cm^{-1} (OAc).

Anal. Calc. for $C_{25}H_{30}N_2O_{12}$: C, 54.54; H, 5.45; N, 5.09. Found: C, 54.53; H, 5.38; N, 4.94.

*2-(*p-*Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole* (**12c**). — *A. From benzaldehyde* (p-*methoxybenzoyl)hydrazone* (**11c**). A solution of **11c** (Ref. 12; 2 g) in dry ether (200 ml) was treated with yellow mercuric oxide (2.5 g), magnesium oxide (0.5 g), and iodine (2 g) for 24 h at room temperature, with occasional shaking. The suspension was then filtered, and the inorganic residue was washed with ether. The filtrate and washings were combined, successively washed with saturated potassium iodide solution, sodium thiosulfate solution, and water, dried (sodium sulfate), and evaporated, to give a residue that crystallized from ethanol, affording 1.2 g of **12c** as needles. m.p. 148°.

Anal. Calc. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.79; N, 10.96.

B. From anisaldehyde benzoylhydrazone. When this hydrazone (1 g) was oxidized in the same way as described in (*A*), it yielded the same product (**12c**), identified by mixed m.p. and comparison of the i.r. spectra.

Found: C, 71.32; H, 4.82; N, 11.30.

*2-(*p-*Chlorophenyl)-5-phenyl-1,3,4-oxadiazole* (**12d**). — Oxidation of benzaldehyde (*p*-chlorobenzoyl)hydrazone (**11d**) with mercuric oxide–iodine gave **12d**; m.p. 130°.

Anal. Calc. for $C_{14}H_9ClN_2O$: C, 65.49; H, 3.50; N, 10.91. Found: C, 65.50; H, 3.75; N, 10.67.

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