109. *Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part V. The Synthesis of* 9-D-*Mannopyranosidoxanthine and of* 9-D-*Ribopyranosidoxanthine.*

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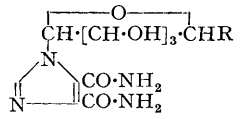
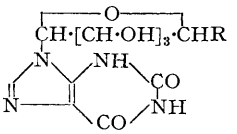
Using the methods developed in previous parts of this series, the xanthine-9-glycosides named in the title have been synthesised.

In Part IV (Baxter and Spring, *J.*, 1947, 378) the preparation of 1-D-glucosido-, 1-D-arabinosido-, 1-L-arabinosido- and 1-D-xylopyranosido-glyoxaline-4 : 5-dicarboxyamide was described. Of these dicarboxyamides, only the last underwent intramolecular ring closure when treated with alkaline potassium hypobromite solution to yield the corresponding 9-substituted xanthine. We have now extended our study to other glycosides.

(I.) 

 (II.)

Treatment of the silver derivative of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-D-mannose gave a gum which could not be crystallised. Treatment of this with ammonia gave 1-D-*mannosidoglyoxaline*-4 : 5-*dicarboxyamide* (I, R = CH_2OH) which on acetylation yielded 1-*tetra-acetyl*-D-*mannosidoglyoxaline*-4 : 5-*dicarboxyamide*. Treatment of 1-D-mannosidoglyoxaline-4 : 5-dicarboxyamide with alkaline potassium hypobromite gave 9-D-*mannopyranosidoxanthine* (II, R = CH_2·OH); this separates with water of crystallisation which was not lost on heating at 135° in a vacuum. Hydrolysis of the glycoside with dilute sulphuric acid gives a mixture of xanthine and D-mannose. The former was characterised by the preparation of its perchlorate and by its ultra-violet absorption spectrum, and the latter by the preparation of its phenylhydrazone. The ultra-violet absorption spectrum of 9-D-mannopyranosidoxanthine in both acid and alkali established the 9-location of the glycosidic group, and periodate oxidation showed this to be of the pyranose form.

Condensation of the silver derivative of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-D-ribose gave a syrup which, after treatment with methanolic ammonia followed by acetylation of the product with acetic anhydride in pyridine, yielded 1-*triacetyl*-D-*ribosidoglyoxaline*-4 : 5-*dicarboxyamide* which on treatment with methanolic ammonia yielded 1-D-*ribosidoglyoxaline*-4 : 5-*dicarboxyamide* (I, R = H). Treatment of this with alkaline potassium hypobromite solution followed by addition of alcohol to the reaction mixture precipitated a beautifully crystalline *potassium* salt of 9-D-ribosidoxanthine, which was characterised as a 9-riboside by its absorption spectrum. Hydrolysis of this salt with dilute sulphuric acid gave a mixture of xanthine (characterised by its absorption spectrum and by the preparation of its perchlorate) and ribose (characterised by the preparation of ribosazone). The potassium salt was converted into the corresponding lead salt which, when treated with hydrogen sulphide, gave 9-D-*ribopyranosidoxanthine* (II, R = H) which separates from aqueous alcohol with water of crystallisation; periodate oxidation shows the glycosidic group to be of the pyranose type.

Experimental.

1-D-*Mannosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A suspension of the silver derivative of methyl glyoxaline-4 : 5-dicarboxylate (9·3 g.) in sulphur-free xylene (300 c.c.) was treated with a solution of freshly prepared acetobromo-D-mannose (from 15 g. of β-penta-acetyl D-mannose) in hot xylene (50 c.c.) and the mixture heated under reflux until the solution no longer gave a positive halogen test. Silver bromide was removed, and the filtrate, after cooling and removal of a small quantity of methyl glyoxaline-4 : 5-dicarboxylate, evaporated to dryness under reduced pressure. The residual syrup could not be crystallised. It was dissolved in methanol (45 c.c.) and the solution saturated with ammonia at 0° and kept at this temperature for 48 hours. The ammonia and some methanol were removed under reduced pressure and the crystalline solid collected and recrystallised from aqueous methanol to give 1-D-*mannosidoglyoxaline*-4 : 5-*dicarboxyamide* as needles, m.p. 208—210° (decomp.), $[\alpha]_D^{15°}$ −4° (*l*, 2; *c*, 1·3 in water) (Found : C, 41·8; H, 5·4; N, 17·5. $C_{11}H_{16}O_7N_4$ requires C, 41·8; H, 5·1; N, 17·7%).

1-*Tetra-acetyl*-D-*mannosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of 1-D-mannosidoglyoxaline-4 : 5-dicarboxyamide (1 g.) in pyridine (5 c.c.) and acetic anhydride (5 c.c.) was kept at 0° for 48 hours. The product was crystallised from aqueous ethanol to yield 1-*tetra-acetyl*-D-*mannosidoglyoxaline*-4 : 5-*dicarboxyamide* as small prisms (1 g.), m. p. 184—185° (Found : C, 47·4; H, 5·1; N, 11·6. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·0; N, 11·6%).

9-D-*Mannosidoxanthine*.—1-D-Mannosidoglyoxaline-4 : 5-dicarboxyamide (1·0 g.) was treated at 0° with a freshly prepared alkaline solution of potassium hypobromite obtained as described in Part IV (5·6 c.c. ≡ 1 mol. of KOBr) and kept at this temperature for 1¼ hours. The solution was heated on the steam-bath for a few minutes to decompose the excess hypobromite, and after cooling was acidified with acetic acid. After 16 hours at 0° the crystalline solid was collected (0·4 g.), a further small quantity (50 mg.) separating from the mother liquors on prolonged standing at 0°. After recrystallisation from aqueous ethanol 9-D-*mannosidoxanthine* was obtained as small elongated prisms which did not melt but partly decomposed between 300° and 360°. It gives an insoluble lead salt and a positive Molisch reaction. It is readily soluble in warm water but insoluble in the common organic solvents. $[\alpha]_D^{10°}$ +96° (*l*, 1; *c*, 0·5 in water) (Found : C, 37·4; H, 5·2; N, 16·3. $C_{11}H_{14}O_7N_4,2H_2O$ requires C, 37·7; H, 5·1; N, 16·0%). Light absorption : (*a*) In N/10-hydrochloric acid, maxima at 2350 A. (ε = 10,900) and 2610 A. (ε = 10,900); (*b*) in N/10-sodium hydroxide, maxima at 2490 A. (ε = 12,000), and 2770 A. (ε = 10,600).

Hydrolysis. The mannoside (200 mg.) was heated under reflux with N/2-sulphuric acid (7 c.c.). After 1 hour the separated xanthine was collected (75 mg.) and characterised by the preparation of the perchlorate which separated as plates, m.p. 257—258° (decomp.) either alone or when mixed with an authentic specimen. Light absorption in N/10-sodium hydroxide : Maximum at 2850 A. (ε = 8,600). The filtrate obtained after the separation of xanthine was exactly neutralised by the addition of sodium hydroxide solution and the solution treated with phenylhydrazine in aqueous acetic acid at 50° for 1 hour. After cooling the solid was collected and recrystallised from water to give D-mannose phenylhydrazone as microscopic prisms, m. p. 183° (decomp.) either alone or when mixed with an authentic specimen.

1-*Triacetyl*-D-*ribosidoglyoxaline*-4 : 5-*dicarboxyamide*.—β-Tetra-acetyl D-ribose (5 g.) (Levene and Tipson, *J. Biol. Chem.*, 1931, **92**, 109) was dissolved in glacial acetic acid (25 c.c.), saturated with dry hydrogen bromide at 0°, and kept at room temperature for 1 hour. The hydrogen bromide was removed at room temperature under reduced pressure, and the solution diluted with sulphur-free toluene (3 × 100 c.c.) and evaporated to a thick syrup, the temperature being maintained below 35°. This syrup crystallised to yield acetobromo-D-ribose as prisms from ether–light petroleum (b. p. 40—60°), m. p. 96°. Since we found that the crystalline acetobromo-sugar quickly decomposed on attempted dissolution in hot xylene, it was advantageous to use the crude syrup which is more readily soluble in xylene. A solution of the syrup (from 5 g. of tetra-acetyl D-ribose) in sulphur-free xylene (100 c.c.) was added to a suspension of the silver derivative of methyl glyoxaline-4 : 5-dicarboxylate (from 3·1 g. of methyl glyoxaline-4 : 5-dicarboxylate). The mixture was boiled for 10 minutes, after which the solution no longer gave a positive halogen test. The cooled mixture was filtered, and the filtrate evaporated under reduced pressure to yield a thick syrup. The syrup was dissolved in methanol (100 c.c.), and the solution saturated with dry ammonia at 0° and kept for 24 hours at room temperature. Evaporation of this solution gave a syrup which failed to crystallise. It was dissolved in dry pyridine (15 c.c.) and acetic anhydride (15 c.c.), and kept at 0° for 12 hours. Ethanol (50 c.c.) was added with cooling, and the mixed solvents were removed under reduced pressure; the residue then crystallised. Recrystallisation from ethanol yielded 1-*triacetyl*-D-*ribosidoglyoxaline*-4 : 5-*dicarboxyamide* as prismatic needles, m. p. 246—248°, $[\alpha]_D^{17°}$ +55° (*l*, 1; *c*, 2·0 in chloroform) (Found : C, 47·1; H, 5·0; N, 13·2. $C_{16}H_{20}O_9N_4$ requires C, 46·6; H, 4·9; N, 13·6%).

1-D-*Ribosidoglyoxaline*-4 : 5-*dicarboxyamide*.—The triacetyl-D-riboside (1 g.) was deacetylated by treatment with methanolic ammonia in the usual manner. 1-D-*Ribosidoglyoxaline*-4 : 5-*dicarboxyamide* separated from aqueous ethanol as needles (0·65 g.), m. p. 215—216°, $[\alpha]_D^{17°}$ +17° (*l*, 1; *c*, 1·0 in water). It is readily soluble in water and insoluble in ethanol (Found : C, 42·0; H, 5·1. $C_{10}H_{14}O_6N_4$ requires C, 42·0; H, 4·9%).

9-D-*Ribosidoxanthine*.—1-D-Ribosidoglyoxaline-4 : 5-dicarboxyamide (0·5 g.) was shaken with potassium hypobromite solution (2·7 c.c.) at 0°. After 1 hour at 0°, a few drops of alcohol were added, the potassium salt of 9-D-ribosidoxanthine (200 mg.) separating as needles which, after recrystallisation from aqueous ethanol, had m. p. 295—300° (decomp.), $[\alpha]_D^{16°}$ −12° (*l*, 1; *c*, 1·0 in water) (Found : C, 33·8; H, 4·1; N, 15·3, 15·9. $C_{10}H_{11}O_6N_4K,2H_2O$ requires C, 33·5; H, 4·2; N, 15·6%). The potassium salt (100 mg.) in water (5 c.c.) was treated dropwise with a saturated solution of lead acetate and dilute ammonia until no further precipitate formed with either reagent. The lead salt was collected, washed with water, suspended in hot water (100 c.c.), and decomposed by a stream of hydrogen sulphide. The precipitate was filtered, and the solid again suspended in water and treated with hydrogen sulphide. The combined filtrates were evaporated to 5 c.c. bulk, and the solution was diluted with ethanol (5 c.c.) and kept at 0°; 9-D-*ribosidoxanthine* then separated as fine needles (48 mg.) which did not melt below

360°, $[\alpha]_D^{16°}$ −10° (*l*, 1; *c*, 0·3 in water) (Found: C, 39·9; H, 4·9; N, 18·1. $C_{10}H_{12}O_6N_4,H_2O$ requires C, 39·7; H, 4·6; N, 18·5%). Light absorption: (*a*) In N/10-sodium hydroxide, maxima at 2490 A. (ε = 11,000) and 2780 A. (ε = 9,600); (*b*) in N/10-hydrochloric acid, maxima at 2340 A. (ε = 10,400) and 2620 A. (ε = 10,400).

Hydrolysis. The potassium salt of 9-D-ribosidoxanthine (70 mg.) was refluxed with N/2-sulphuric acid (5 c.c.) for 2 hours. The separated xanthine (20 mg.) was collected and characterised by the preparation of the perchlorate, m. p. and mixed m. p. 260°, and by its ultra-violet light absorption in N/10-sodium hydroxide solution (maximum at 2840 A., ε = 9,400). The filtrate obtained after the removal of xanthine was exactly neutralised with sodium carbonate solution and treated with excess of phenylhydrazine in dilute acetic acid; ribosazone (10 mg.) separated as micro-needles, m.p. 160—162° not depressed when mixed with an authentic specimen.

Periodate Oxidations.—The oxidations were carried out as described in Part IV.

Compound.	Formic acid (mols. per mol.).	Periodate consumed (mols. per mol.).
9-D-Mannosidoxanthine	1·05	2·0
1-D-Ribosidoglyoxaline-4 : 5-dicarboxyamide	1·0	2·08
9-D-Ribosidoxanthine	1·06	2·04

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