76. *Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part IV. The Synthesis of* 9-d-*Xylopyranosidoxanthine.*

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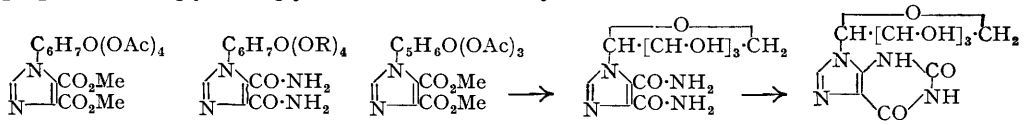
Treatment of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-*d* xylose gives *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* (III) which on treatment with alcoholic ammonia yields 1-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* (IV). Treatment of the latter with alkaline potassium hypobromite solution gives 9-d-*xylopyranosidoxanthine* (V) in good yield.

When the work described in this series of papers was first envisaged, one of the principal objectives was to attempt to apply the intramolecular Hofmann reaction to a suitably substituted glyoxaline dicarboxyamide to effect a synthesis of a purine glycoside of the xanthosine (9-*d*-ribofuranosidoxanthine) type. It was appreciated that at least three major hurdles would have to be negotiated before this could be achieved. First, such a synthesis would require that a 1-substituted glyoxaline-4 : 5-dicarboxyamide should give mainly a 9-substituted xanthine rather than the 7-substituted isomer. Secondly, it would require the development of a method for the introduction of a suitable glycosidic group at position 1 in glyoxaline-4 : 5-dicarboxyamide and, thirdly, it required the establishment of conditions for the intramolecular ring closure of this glycoside. In Part II (Baxter and Spring, *J.*, 1945, 232) we described the synthesis in high yield of 9-methylxanthine from 1-methylglyoxaline-4 : 5-dicarboxyamide, a reaction which encouraged us to believe that the first hurdle had been successfully negotiated and led us to turn our attention to a study of the preparation and properties of 1-glycosidoglyoxaline-4 : 5-dicarboxyamides.

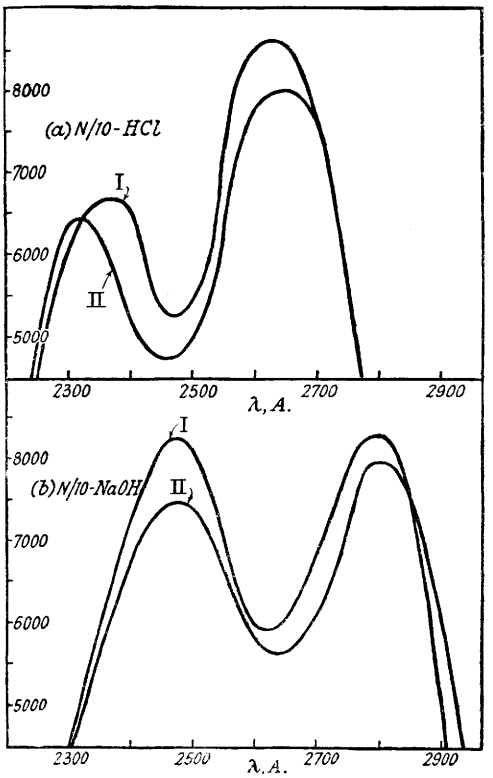


(I.) (II.) (III.) (IV.) (V.)

Treatment of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate (Baxter and Spring, *loc. cit.*) with acetobromo-*d*-glucose gave *methyl* 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate* (I). The reaction proceeds smoothly to give excellent yields if the silver salt is obtained in a granular form and special precautions are observed to ensure purity of materials (cf. Gulland and Macrae, *J.*, 1933, 662). When the glucoside (I) is treated with methanolic ammonia, simultaneous deacetylation and amidation occur to give 1-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* (II, R = H) which, when treated with acetic anhydride and pyridine, yields 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* (II, R = Ac). Condensation of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with the appropriate acetobromo-sugar followed by treatment of the product with methanolic ammonia gave 1-l- and 1-d-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*; acetylation of the 1-*l*-isomer yielded 1-*triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*. Acetylation of the 1-*d*-isomer gave an oil which could not be crystallised. Condensation of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-*d*-xylose gave *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* (III) which with alcoholic ammonia yielded 1-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* (IV). Acetylation of the latter compound gave 1-*triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.

Treatment of 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (II, R = H) with alkaline potassium hypobromite under the conditions employed in the preparation of 9-methylxanthine *loc. cit.*) gave a glycosidic product which was isolated by precipitation as a barium salt; the extremely low yield, however, did not allow further purification or characterisation. Many variations in reaction conditions were made, including the use of barium hypobromite with the

object of achieving rapid separation of the barium salt of the purine glycoside from the reaction mixture; all these attempts were unsuccessful. 1-Tetra-acetyl-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (II, R = Ac) was recovered unchanged after treatment with alkaline potassium hypobromite solution. Treatment of 1-*l*-arabinosidoglyoxaline-4 : 5-dicarboxyamide with alkaline potassium hypobromite gave a very small yield of a product which appeared to be a 9-glycosidoxanthine since it gave a positive Molisch reaction and its ultra-violet absorption spectrum was very similar to that of 9-methylxanthine. The low yield, however, precluded a successful purification and, as in the previous case, variations in reaction conditions did not lead to an improvement in yield. A similar behaviour was observed in the case of 1-*d*-arabinosidoglyoxaline-4 : 5-dicarboxyamide. 1-Triacetyl-*l*-arabinosidoglyoxaline-4 : 5-dicarboxyamide, which is very insoluble in water, was recovered unchanged after treatment with alkaline potassium hypobromite.



I. 9-*Methylxanthine.*
II. 9-d-*Xylopyranosidoxanthine.*

Treatment of 1-*d*-xylopyranosidoglyoxaline-4 : 5-dicarboxyamide with alkaline potassium hypobromite gave 9-d-*xylopyranosidoxanthine* (V) in good yield. The glycoside (V) crystallises from water in well-formed microscopic needles which slowly decompose on heating above 250°. Hydrolysis of 9-*d*-xylopyranosidoxanthine with dilute sulphuric acid gives a mixture of *d*-xylose (characterised as its tetra-acetyl derivative) and xanthine. The latter was characterised by the preparation of its perchlorate and by its ultra-violet absorption spectrum. The ultra-violet absorption spectra of 9-*d*-xylopyranosidoxanthine in both acid and alkali (see fig.) are virtually identical with those of 9-methylxanthine (see fig.) and with those of xanthosine (Gulland, Holiday, and Macrae, *J.*, 1934, 1643) and show that the synthetic material is a 9- and not a 7-glycosidoxanthine.

Oxidation of the synthetic 9-xylosidoxanthine and of the parent 1-*d*-xylosidoglyoxaline-4 : 5-dicarboxyamide with periodate (Lythgoe and Todd, *J.*, 1944, 592) shows that the glycosidic residue in both compounds is of the pyranose form. We believe that the glycoside residues in all the 1-glycosidoglyoxaline-4 : 5-dicarboxyamides described in this paper are of the pyranose form although this has only been rigorously established in the case of the *d*-xyloside.

The behaviour of 9-*d*-xylopyranosidoxanthine, xanthosine, and 9-methylxanthine when treated with acetic anhydride will form the subject of a later communication.

Experimental.

Methyl 1-*Tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate*.—A solution of methyl glyoxaline-4 : 5-dicarboxylate (Baxter and Spring, *loc. cit.*) (6·1 g.) in aqueous methanol (50%; 300 c.c.) was treated at 50° with one of silver nitrate (5·7 g.) in water (50 c.c.), added rapidly with stirring. The mixture was made just alkaline by the addition of dilute aqueous ammonia (10 c.c., of *d* 0·88 in 90 c.c. of water) and kept at 55—60°, the precipitated silver salt then becoming granular. The mixture was cooled in the dark, the silver salt collected, washed successively with water, methanol, and ether, and dried in a vacuum in the dark (yield 9·4 g.). The silver salt was suspended in sulphur-free xylene (350 c.c.), and the suspension finally dried in the usual manner by removal of solvent (approx. 50 c.c.) through a Fenské-type column. To the resulting suspension was added freshly prepared acetobromo-*d*-glucose (12·5 g.), and the mixture refluxed in an oil-bath at 180° until the solution no longer gave a positive halogen test (approx. 15 mins.). The mixture was filtered, cooled to 45°, and filtered again to remove a small quantity of methyl glyoxaline-4 : 5-dicarboxylate. The filtrate was evaporated under reduced pressure, and the residual gum dissolved in hot methanol (150 c.c.). On cooling *methyl* 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate* separated as prisms (10 g.) which after a recrystallisation had m. p. 123°, $[\alpha]_D^{19°}$ + 16° (l = 1, c = 2·5 in chloroform) (Found: C, 48·6; H, 4·8; N, 5·4. $C_{21}H_{26}O_{13}N_2$ requires C, 49·0; H, 5·1; N, 5·4%).

1-d-*Glucosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of the above tetra-acetyl derivative (6·5 g.) in dry methanol (150 c.c.) was saturated with dry ammonia at 0° and kept at this temperature for 48 hours. The ammonia and some methanol were removed under reduced pressure, the amide (4·5 g.) rapidly separating. After recrystallisation from pyridine 1-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as small needles, m. p. 232—233° (decomp.). This diamide (2·5 g.) was also prepared by similar treatment of the gum obtained by evaporation of the original methanolic mother-liquor from the crystallisation of methyl 1-tetra-acetyl-*d*-glucosidoglyoxaline-4 : 5-dicarboxylate. The amide is slightly soluble (1%) in water and insoluble in ethanol. When crystallised from aqueous ethanol, it separates as a *monohydrate* which forms feathery needles, m. p. 146—148°. The water of crystallisation was not lost on drying at 135°/10^{-2} mm. for 6 hours [Found (m. p. 232—233°): C, 42·0; H, 5·2. $C_{11}H_{16}O_7N_4$ requires C, 41·8; H, 5·1%. Found (m. p. 146—148°): C, 39·2; H, 5·1; N, 16·3. $C_{11}H_{16}O_7N_4,H_2O$ requires C, 39·5; H, 5·4; N, 16·8%].

1-*Tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of anhydrous 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (4·5 g.) in pyridine (25 c.c.) and acetic anhydride (25 c.c.) was kept at 0° for 24 hours, and then heated on a water-bath for 10 minutes and carefully diluted with ethanol (50 c.c.). The mixture was concentrated under reduced pressure until crystallisation commenced; the acetyl derivative separated from this mixed solvent as long needles containing pyridine of crystallisation which was lost on crystallisation from methanol, from which 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as prisms (5·1 g.), m. p. 162—163°. This diamide is insoluble in water, moderately soluble in methanol, and readily soluble in chloroform and benzene (Found: C, 46·8; H, 5·3; N, 11·3. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·1; N, 11·6%). When treated with methanolic ammonia by the method described in the previous paragraph, it was converted into 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide, m. p. 232—233° (decomp.). Acetylation of hydrated 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide, m. p. 146—148°, by the same method, also gave this tetra-acetyl derivative, m. p. and mixed m. p. 162—163° (decomp.).

1-l-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*.—The silver salt of methyl glyoxaline-4 : 5-dicarboxylate was prepared as described previously from the ester (9·2 g.) and silver nitrate (8·5 g.), and dried by the xylene method. A suspension of the silver salt in boiling xylene (400 c.c.) was treated with a solution of acetobromo-*l*-arabinose (13 g.) in hot xylene (100 c.c.), and the mixture heated under reflux for 10 minutes; reaction was then complete. The mixture was filtered, and the filtrate evaporated under reduced pressure to yield a gum which could not be crystallised. A solution of this gum in methanol (200 c.c.) was saturated with dry ammonia at 0° and then kept at 0° for 24 hours. The crystalline mass which had separated was collected and crystallised from aqueous alcohol, from which 1-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as needles (8·2 g.) sintering at 175—180° and melting at 215—216° (decomp.); $[\alpha]_D^{22°}$ + 44° (l = 1, c = 1·5 in pyridine) (Found: C, 40·8; H, 5·3; N, 18·5. $C_{10}H_{14}O_6N_4,\frac{1}{2}H_2O$ requires C, 40·7; H, 5·1; N, 19·0%).

1-*Triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*.—1-l-Arabinosidoglyoxaline-4 : 5-dicarboxyamide was acetylated at 0° by treatment with pyridine (5 c.c.) and acetic anhydride (5 c.c.). The product was crystallised first from ethanol and then from ether–light petroleum (b. p. 40—60°) to give 1-*triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* as plates, m. p. 132—133° (Found: C, 46·6; H, 5·0. $C_{16}H_{20}O_9N_4$ requires C, 46·6; H, 4·9%).

1-d-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* was obtained from acetobromo-*d*-arabinose and the silver salt of methyl glyoxaline-4 : 5-dicarboxylate by the method described for the *l*-isomer. It separated from aqueous ethanol as needles, m. p. 216° (sintering at 175—180°), $[\alpha]_D^{19°}$ − 40° (l = 1, c = 1·7 in pyridine). As in the case of the *l*-isomer it separates with water of crystallisation which is very tenaciously held (Found: C, 41·0; H, 5·0; N, 18·9. $C_{10}H_{14}O_6N_4,\frac{1}{2}H_2O$ requires C, 40·7; H, 5·1; N, 19·0%).

Methyl 1-*Triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate*.—Condensation of the dry silver salt of methyl glyoxaline-4 : 5-dicarboxylate (from 11 g. of ester) with acetobromo-*d*-xylose (16·5 g.) in sulphur-free, dry xylene (600 c.c.) was effected in the manner previously described. After removal of silver bromide, the filtrate was cooled; the product then separated, and recrystallisation from methanol gave *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* as needles (10 g.), m. p. 166—167°, $[\alpha]_D^{20°}$ + 22·6° (l = 1, c = 1·8 in chloroform) Found: C, 49·0; H, 5·1. $C_{18}H_{22}O_{11}N_4$ requires C, 48·9; H, 5·0%).

1-d-*Xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.—Methyl 1-triacetyl-*d*-xylosidoglyoxaline-4 : 5-dicarboxylate (8·5 g.) was dissolved in methanol (200 c.c.) saturated with dry ammonia at 0°. The solution was kept at room temperature for 18 hours. The ammonia was removed under reduced pressure, and the product then crystallised. Recrystallisation from aqueous ethanol gave 1-*d*-xylopyranosidoglyoxaline-4 : 5-dicarboxyamide as needles (4·5 g.) sintering at 165—170° and melting at 224—225° (decomp.), $[\alpha]_D^{19°}$ + 34° (l = 4, c = 0·3 in water). The amide separated as a *monohydrate* and the water of crystallisation was not lost on drying for 8 hours at 135° in a high vacuum over phosphoric oxide (Found : C, 39·9; H, 5·1; N, 18·3. $C_{10}H_{14}O_6N_4,H_2O$ requires C, 39·5; H, 5·3; N, 18·4%). Removal of the solvent from the original xylene mother-liquor of methyl 1-triacetyl-*d*-xylosidoglyoxaline-4 : 5-dicarboxylate gave a gum which on treatment with methanolic ammonia as described above gave a further quantity (5 g.) of this diamide, m. p. 224—225° (sintering at 165—170°).

1-*Triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.—1-*d*-Xylopyranosidoglyoxaline-4 : 5-dicarboxyamide (1 g.) was acetylated by treatment with pyridine (5 c.c.) and acetic anhydride (5 c.c.) by the method previously described. After addition of ethanol and removal of the mixed solvent under reduced pressure, the residue was crystallised from ethanol, from which 1-*triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as needles (1·1 g.), m. p. 158—159° (Found : C, 46·2; H, 4·9; N, 13·1. $C_{10}H_{20}O_8N_4$ requires C, 46·6; H, 4·9; N, 13·6%).

Treatment of 1-l-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide with Alkaline Potassium Hypobromite*.—The hypobromite solution used in this and the following experiment was prepared by adding bromine (10·7 g.) dropwise to a solution of potassium hydroxide (16·8 g.) in water (100 c.c.) at 0°. The hypobromite content of this solution was estimated by titration with sodium thiosulphate immediately before use. It decomposed very slowly on storing at 0° but more concentrated solutions deteriorated rapidly. The amide (1 g.) was treated with one molecular proportion of the hypobromite solution at 0°, and the solution was kept at 0° for 30 minutes and then heated at 60° for 3 minutes; hypobromite could then no longer be detected. The solution was cooled and acidified to litmus by means of acetic acid. After standing for several days, the amorphous solid which had separated was collected; it gave a positive Molisch test and an insoluble lead salt. When heated, it exhibited marked swelling at 240—245° and more definite decomposition at 260°. Analysis indicated the presence of inorganic matter. Light absorption : (*a*) In N/10-hydrochloric acid; maxima at 2260 A., ε = 6800, and 2637 A., ε = 6400. (*b*) In N/10-sodium hydroxide; maxima at 2415 A., ε = 4900, and 2810 A., ε = 4600.

9-d-*Xylopyranosidoxanthine*.—1-*d*-Xylosidoglyoxaline-4 : 5-dicarboxyamide (1 g.) was treated with alkaline hypobromite solution (6 c.c.) and kept at 0° for 30 minutes and then at 60° for a few minutes until the solution no longer contained hypobromite. The solution was cooled, acidified with acetic acid, and the precipitated solid (0·5 g.) collected. This solid gave a positive Molisch test and an insoluble lead salt. After three crystallisations from water 9-d-*xylopyranosidoxanthine* was obtained as microscopic needles, $[\alpha]_D^{17°}$ — 15° (l = 1, c = 1·4 in water). The crystallisations were attended with much loss of material. 9-*d*-Xylopyranosidoxanthine does not exhibit a definite m. p., but gradually decomposes on heating above 250°; it is quite soluble in water but insoluble in the common organic solvents. For analysis, the air-dried material was further dried at 118°/10^{-3} mm. over phosphoric oxide for 2 hours (Found : C, 41·8; H, 4·6; N, 20·0. $C_{10}H_{12}O_6N_4$ requires C, 42·3; H, 4·2; N, 19·7%). Light absorption : (*a*) In N/10-hydrochloric acid; maxima at 2335 A., ε = 6500, and 2645 A., ε = 8000. (*b*) In N/10-sodium hydroxide; maxima at 2480 A., ε = 7500, and 2805 A., ε = 8000.

Hydrolysis of 9-d-*Xylopyranosidoxanthine*.—The xyloside (0·35 g.) was heated under reflux with aqueous N/2-sulphuric acid (10 c.c.). After a short time xanthine separated and the reaction was complete after 1 hour. The xanthine (0·15 g.) was collected; it was insoluble in water and dilute acids but freely soluble in alkali and dilute aqueous ammonia, separating from the latter on boiling the solution. It decomposed at about 360° (Found : C, 39·2; H, 2·8. Calc. for $C_5H_4O_2N_4$: C, 39·5; H, 2·6%). Light absorption in N/10-sodium hydroxide : maximum at 2845 A., ε = 8000. A specimen of xanthine prepared for comparison by Traube's method (*Ber.*, 1900, **33**, 3045) exhibited a maximum at 2845 A., ε = 8000. The hydrolysis product was further characterised by conversion into its perchlorate, which formed plates which decomposed at 260°.

The filtrate obtained after removal of xanthine was exactly neutralised by addition of sodium hydroxide, and the solution evaporated to dryness. The residue was refluxed with acetic anhydride (4 c.c.) and sodium acetate (0·1 g.) for 1 hour. The product was isolated in the usual manner, and crystallised from aqueous ethanol to give β-tetra-acetyl *d*-xylose as needles, m. p. 124—125° either alone or when mixed with an authentic specimen.

Periodate Oxidations.—The compound (*ca.* 40 mg.) in water (50 c.c.) was treated with sodium metaperiodate solution (0·235M; 10 c.c.), and the solution kept at 20° for 36 hours. A sample of the solution (20 c.c.) was withdrawn and, after the addition of ethylene glycol (1 c.c.) to decompose excess of periodate (which has an acid reaction), titrated against N/100-barium hydroxide solution with methyl-red as indicator. A second sample of the solution (20 c.c.) was made alkaline by addition of sodium bicarbonate solution, and the unchanged metaperiodate estimated in the usual manner :

Compound.	Formic acid (mols. per mol.).	Periodate consumed (mols. per mol.).
1-*d*-Xylosidoglyoxaline-4 : 5-dicarboxyamide	1·01	2·02
9-*d*-Xylosidoxanthine	0·9	1·85
9-Methylxanthine	0	0

It is a pleasure to acknowledge our indebtedness to Dr. A. E. Gillam, who measured the ultra-violet absorption spectra, and to Dr. J. K. N. Jones for assistance with the periodate oxidations.

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