55. *Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part VI. Experiments on the Synthesis of Purine Nucleosides. Part XXI. A Synthesis of Xanthosine.*

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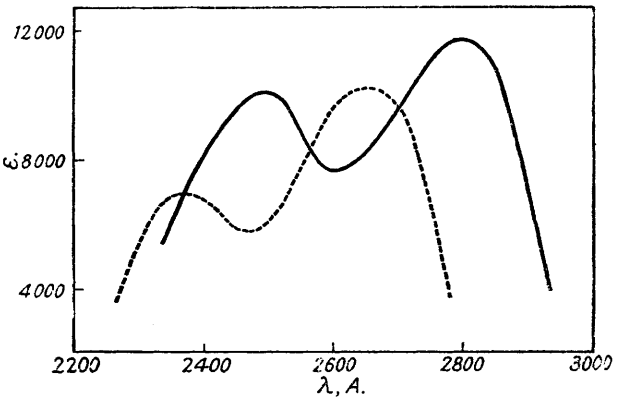
The synthesis of 9-D-ribofuranosidoxanthine, identical with xanthosine from natural sources, is described.

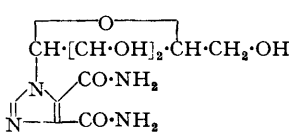
The first series of papers named in the title describes the development of a route for the synthesis of purine glycosides of the xanthosine (9-D-ribofuranosidoxanthine) type. Initially, it was shown that treatment of glyoxaline-4 : 5-dicarboxyamide with alkaline hypobromite gave xanthine, and that similar treatment of 1-methylglyoxaline-4 : 5-dicarboxyamide gave 9-methylxanthine and not 7-methylxanthine (Baxter and Spring, *J.*, 1945, 232). This fortunate behaviour led to a synthesis of 9-glycosidoxanthines in which the requisite glyoxaline-4 : 5-dicarboxyamide was prepared by treatment of the silver derivative of methyl glyoxaline-4 : 5-

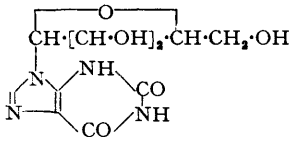
dicarboxylate with the appropriate acetobromo-sugar followed by reaction of the product with ammonia. Each of the 1-glycosidoglyoxaline-4 : 5-dicarboxyamides so obtained is of the pyranose type. Of the various 1-glycosidoglyoxaline-4 : 5-dicarboxyamides obtained, the 1-D-xylopyranosido-, 1-D-mannopyranosido-, and 1-D-ribopyranosido-derivatives were successfully converted into the corresponding 9-D-glycopyranosidoxanthines by treatment with alkaline hypobromite (Baxter and Spring, *loc. cit.*; *J.*, 1947, 378; Baxter, McLean, and Spring, *J.*, 1948, 523).



Absorption Spectrum of Synthetic Xanthosine {0·1N-NaOH ——— 0·1N-HCl - - - - - -

Methods for the synthesis of purine nucleosides have been the subject of investigations described in the second series of papers named in the title. A related investigation disclosed a method for the preparation of acetobromoribofuranose in which 1 : 2 : 3 : 5-tetra-acetyl D-ribofuranose is treated with hydrogen bromide and which has been used to effect a synthesis of the natural nucleosides cytidine (Howard, Lythgoe, and Todd, *J.*, 1947, 1052), adenosine (Davoll, Lythgoe, and Todd, *J.*, 1948, 967), and guanosine (*idem, ibid.*, p. 1685).

(I.) 



(II.)

It was agreed to join these two series of investigations in an attempt to synthesise xanthosine. Condensation of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo- or acetochloro-D-ribofuranose gave a product which could not be obtained in a crystalline form. The product (from acetochloro-D-ribofuranose) was treated with ammonia to yield 1-D-*ribofuranosidoglyoxaline*-4 : 5-*dicarboxyamide* (I). Treatment of (I) with alkaline hypobromite solution gave an amorphous potassium salt. The potassium salt was converted into the corresponding lead salt, and the latter decomposed by means of hydrogen sulphide to yield xanthosine (II) as fine needles. It gave a positive Molisch test and was characterised by its ultra-violet absorption spectrum in acid and alkaline solution (see Fig.; cf. Gulland, Holiday, and Macrae, *J.*, 1934, 1639). Titration with periodate confirmed the furanose form of the glycosidic group, and confirmation of the identity of the synthetic xanthosine with that of a sample from natural sources was obtained by comparison of *X*-ray powder photographs which were identical; we are indebted to Dr. J. H. A. Clews for these measurements.

Experimental.

1-D-*Ribofuranosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of 1 : 2 : 3 : 5-tetra-acetyl D-ribofuranose (2·75 g.; Howard, Lythgoe, and Todd, *loc. cit.*) in dry ether (50 c.c.), which had been saturated with dry hydrogen chloride at 0°, was set aside at 0° for 3 days, and then evaporated under reduced pressure at 15°. The residual crude acetochloro-sugar was taken up in a little dry xylene and added to a suspension of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate (3·5 g.; Baxter and Spring, 1945, *loc. cit.*) in xylene (50 c.c.) which had been dried by azeotropic distillation, and the mixture was heated under reflux in an oil-bath at 180° for 2 hours and filtered hot, and the filter residue washed with hot xylene. Addition of light petroleum to the cooled filtrate and washings precipitated a yellow resin.

The supernatant liquid was removed by decantation, and the gum washed with light petroleum and dissolved in the minimum amount of hot methanol. A quantity of methyl glyoxaline-4 : 5-dicarboxylate, which separated when the solution was cooled, was removed by filtration. Evaporation of the filtrate gave a yellow gum (1·9 g.) which could not be crystallised; it was dissolved in ethanolic ammonia (30 c.c. saturated at 0°), and the solution set aside for 4½ days. Evaporation under reduced pressure yielded a gelatinous residue which was dissolved in hot water (6 c.c.), treated with charcoal, and allowed to cool. The crystalline material (0·5 g.; m. p. *ca.* 200°) which separated was recrystallised several times from water giving 1-D-*ribofuranosidoglyoxaline*-4 : 5-*dicarboxyamide* (0·35 g.) as colourless needles, m. p. 218—220° (rapid heating), $[\alpha]_D^{15^\circ}$ −16° (±5°) (*c*, 0·276 in pyridine). Periodate titration: 10·6 mg. consumed periodate equivalent to 0·84 c.c. of 0·0985N-sodium arsenite in 69 hours, *i.e.*, uptake corresponding to 1·1 mols. of periodate per mol. of glycoside (Found in material dried at 100°/10^{-2} mm.: C, 42·4; H, 5·2; N, 19·9. $C_{10}H_{14}O_6N_4$ requires C, 42·0; H, 4·9; N, 19·6%).

Xanthosine.—1-D-Ribofuranosidoglyoxaline-4 : 5-dicarboxyamide (400 mg.) was treated at 0° with hypobromite solution [2·4 c.c. (1 mol. of KOBr), prepared as described by Baxter and Spring, *J.*, 1947, 378] with shaking. Solution was soon complete, and the mixture was kept at 0° for 1 hour. After being heated for 4 minutes on the water-bath it was acidified with dilute acetic acid and kept at 0° for 18 hours; a flocculent solid was deposited during this period. Ethanol (0·25 c.c.) was added and the mixture kept at 0° for 2 hours. The solid was collected and dissolved in a little warm water, and the solution filtered and treated with ethanol until it became faintly opalescent. After 3 days at 0°, the amorphous solid was collected and dried in a vacuum over phosphoric oxide (67 mg.); the presence of potassium was established by ignition. A further quantity (30 mg.) of this salt was obtained by treatment of the mother liquor with ethanol.

The potassium salt (97 mg.) was dissolved in the minimum amount of water and treated dropwise with a saturated solution of lead acetate and dilute ammonia solution added alternately until precipitation was complete. The lead salt was washed with water, suspended in warm water, and decomposed by a stream of hydrogen sulphide. The mixture was filtered, and the residue again treated with hydrogen sulphide. The combined filtrates were concentrated to small bulk under reduced pressure. On standing, xanthosine (36 mg.) separated as needles. For analysis, the specimen was twice recrystallised from aqueous ethanol and dried at 110°/0·5 mm. (Found: C, 41·0; H, 4·2; N, 19·3. Calc. for $C_{10}H_{12}O_6N_4,\frac{1}{2}H_2O$: C, 41·0; H, 4·4; N, 19·1%). Periodate oxidation: 4·036 mg. and 4·812 mg. consumed periodate equivalent to 0·26 c.c. and 0·33 c.c. of 0·1N-sodium arsenite in 36 hours, corresponding to a consumption of 0·9 and 1·0 mol. of periodate per mol. of glycoside respectively.

We thank Mr. J. Davoll for preparing a specimen of xanthosine from natural guanosine, and we acknowledge gratefully a Senior Award made to one of us (G. A. H.) by the Department of Scientific and Industrial Research, and the award of a Fellowship to another (A. C. McL.) by the Ferguson Bequest Fund.

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