50. *Constitution of the Purine Nucleosides. Part VI. Adenine Deoxyriboside, Adenine Glucoside, and a Route to the Synthesis of the Naturally Occurring Nucleosides.*

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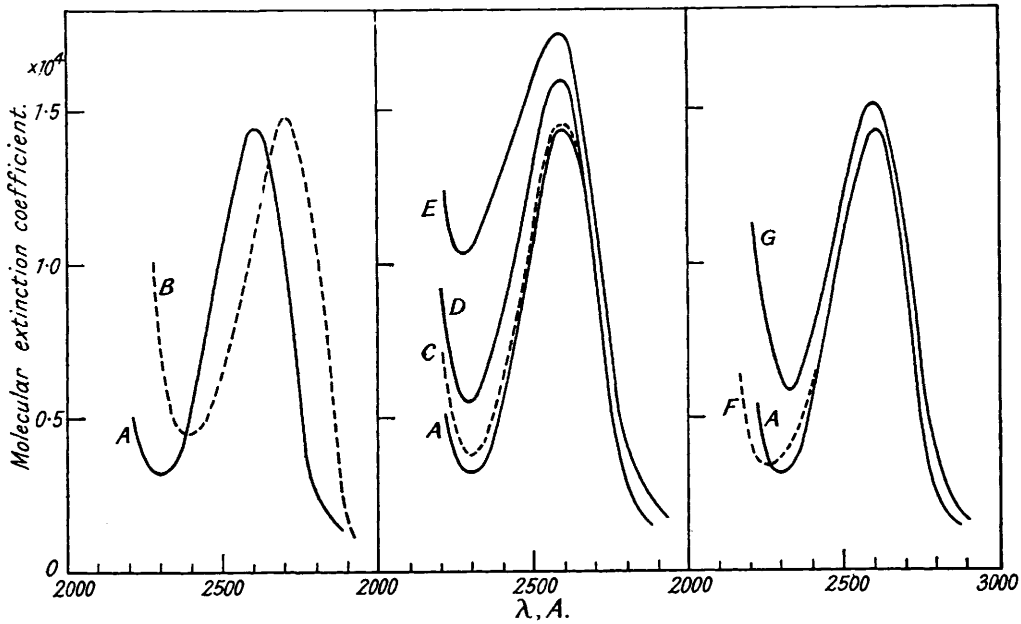
Comparisons of the ultra-violet absorption spectra of adenine deoxyriboside from thymus nucleic acid and of synthetic adenine glucoside with the spectra of 7- and 9-methyladenines show that both these nucleosides are 9-substituted adenines. This means that the purine nucleosides and nucleotides of thymus nucleic acid are similar in constitution to the corresponding derivatives of yeast nucleic acid. It is also important in being the first occasion on which a synthetic purine nucleoside has been recognised as having the carbohydrate radical in the same position as have the natural nucleosides. As a result, a route is open to the synthesis of the naturally occurring nucleosides, and enzyme experiments should shed light on the question of the presence of an α- or a β-glycosidic linkage in these compounds.

IN Parts IV and V (J., **1934**, 1639; **1937**, 1912) the carbohydrate radicals of adenosine and adenine thiomethylpentoside were assigned to the 9-position of the adenine molecule by reason of the close resemblance of their ultra-violet absorption spectra to those of 9-methyladenine, and the dissimilarity of the spectra of 7-methyladenine (Fig. 1; taken from Part IV).

FIG. 1. FIG. 2. FIG. 3.



A. *9-Methyladenine in water,* N/20-HCl *and* N/20-NaOH.

FIG. 1.

B. *7-Methyladenine in water and* N/20-HCl.

FIG. 2.

C. *Adenine deoxyriboside* (M/80,000) *in water.*
D. *Adenine deoxyriboside* (M/75,000) *in* N/20-HCl.
E. *Adenine deoxyriboside* (M/100,000) *in* N/20-NaOH.

FIG. 3.

F. *Adenine* d-*glucoside* (M/80,000) *in water and* N/20-HCl.
G. *Adenine* d-*glucoside* (M/80,000) *in* N/20-NaOH.

The method has now been applied to the determination of the positions of the carbohydrate radicals in adenine deoxyriboside (Klein, *Z. physiol. Chem.*, 1934, **224**, 244) and adenine *d*-glucoside (Fischer and Helferich, *Ber.*, 1914, **47**, 210). Both these are now shown to be 9-substituted adenines.

The interest of these results lies in the following facts. First, the purine nucleosides derived from thymus nucleic acid, and the corresponding nucleotides, are constituted similarly to the nucleosides and nucleotides of yeast nucleic acid as regards the position of the sugar radicals.

Secondly, this is the first occasion on which a synthetic purine nucleoside has been shown to have the carbohydrate radical in the same position as have the natural nucleosides. Theophylline *d*-glucoside and *l*-arabinoside, prepared from silver theophylline and the appropriate acetylated bromo-sugar, are 7-substituted derivatives of theophylline (Gulland, Holiday, and Macrae, J., 1934, 1639), and the same conclusion presumably applies to theophylline rhamnoside (Fischer and Fodor, *Ber.*, 1914, **47**, 1058), *d*-galactoside (Helferich and Kühlewein, *Ber.*, 1920, **53**, 17), *iso*rhamnoside (Fischer, Helferich, and Ostmann, *ibid.*, p. 873), *d*-xyloside and *d*-riboside (Levene and Sobotka, *J. Biol. Chem.*, 1925, **65**, 463), all of which are obtained from theophylline silver.

Thirdly, it follows that dichloroadenine *d*-glucoside and chloroadenine *d*-glucoside (both obtained as intermediates in the preparation of adenine glucoside), hypoxanthine *d*-glucoside (formed from adenine glucoside by the action of nitrous acid), and guanine *d*-glucoside (prepared from chloroadenine glucoside) are all also 9-substituted derivatives. These results provide a route to the synthesis of the naturally occurring purine nucleosides, the appropriate carbohydrate derivatives being used. Moreover, a study of the action of nucleosidases on such synthetic nucleosides should throw light on the question of the presence of an α- or a β-glycosidic linkage in the naturally occurring nucleosides. Experiments along these lines are in progress.

EXPERIMENTAL.

Adenine deoxyriboside, for a pure specimen of which we are much indebted to Dr. W. Klein, was prepared by the fission and dephosphorylation of thymus nucleic acid by a preparation of mixed thymonucleinase and phosphomonoesterase from calf's intestinal mucosa (Klein, *Z. physiol. Chem.*, 1933, **218**, 164) in presence of silver ions, which inhibit the action of the accompanying deaminase. Its ultra-violet absorption spectrum in aqueous solution resembles that of 9-methyladenine, and in acid and in alkaline solutions a slight increase in the value of the extinction coefficient occurs without change of the wave-length (2600 A.) of the peak (Fig. 2), a behaviour similar to that observed in the case of adenine thiomethylpentoside in alkaline solution. It is doubtful whether the measurement of the spectrum in acid solution is valid owing to the ease with which this reagent hydrolyses the glycosidic linkage of adenine deoxyriboside.

For the preparation of adenine glucoside, potassium urate was converted into 2 : 8-dichloroadenine through the stages of 2 : 6-dichloro-8-hydroxypurine and 2 : 6 : 8-trichloropurine (Fischer and Ach, *Ber.*, 1897, **30**, 2208). In the formation of trichloropurine by heating dichlorohydroxypurine with phosphorus oxychloride a silver-lined steel bomb was found to be more convenient than sealed glass tubes, and the use of a mixture of phosphorus trichloride (1 part) and oxychloride (3 parts) instead of pure oxychloride gave better, but fluctuating, yields, although these were never as high as those recorded by Fischer and Ach.

Since the interaction of the sodium salt of dichloroadenine with methyl iodide yields dichloro-9-methyladenine (Fischer, *Ber.*, 1897, **30**, 2238), it seemed possible that the interaction of the silver salt with tetra-acetobromoglucose would also give rise to a 9-substituted compound. The silver salt of dichloroadenine, prepared by the addition of ammoniacal silver nitrate solution to an ammoniacal solution of dichloroadenine, was collected, washed with water, and dried by distillation of its suspension in toluene (Gulland and Macrae, J., 1932, 662). The subsequent condensation with tetra-acetobromoglucose, the deacetylation of the product with methyl-alcoholic ammonia, and the replacement of the chlorine atoms by hydrogen through reduction with hydriodic acid and phosphonium iodide followed the procedures of Fischer and Helferich (*Ber.*, 1914, **47**, 227), the adenine glucoside being finally purified through the picrate. When heated in a melting-point apparatus, the glucoside showed the characteristic behaviour described by Fischer and Helferich.

The ultra-violet absorption spectra of adenine glucoside in aqueous and in acid solutions (peak at 2600 A.) were identical with those of 9-methyladenine; the spectrum in alkaline solution showed a slight increase in the value of the extinction coefficient (Fig. 3).

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