185. *Experiments on the Synthesis of Purine Nucleosides. Part XIX. A Synthesis of Adenosine.*

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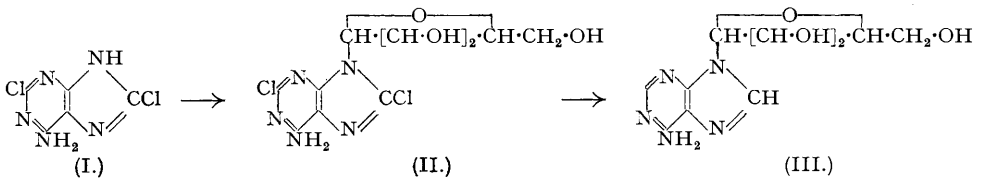
Condensation of the silver salt of 2 : 8-dichloroadenine with crude acetochloro-D-ribofuranose, followed by deacetylation, gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine*. On hydrogenation with a palladised barium sulphate catalyst this compound yielded 9-β-D-*ribofuranosidoadenine*, identical with the natural nucleoside adenosine.

Although our main efforts as described in previous papers of this series have been directed to the development of a general synthetic route for the synthesis of purine nucleosides from appropriate 4-glycosidaminopyrimidines, we have also devoted some attention to other routes which might be of value in individual cases. The method employed by Fischer and Helferich (*Ber.*, 1914, **47**, 210) for the synthesis of adenine glucoside offers one such route, since it has been confirmed that the glucose residue in the synthetic glucoside and the ribose residue in the natural nucleoside adenosine are both located at N_9 in the purine nucleus (Lythgoe, Smith, and Todd, *J.*, 1947, 355; Holland, Lythgoe, and Todd, preceding paper), as was earlier postulated on absorption-spectrum evidence (Gulland and Holiday, *J.*, 1936, 765), and since we have shown that both glycosides have the same configuration (almost certainly β) at the glycosidic linkage (Davoll, Lythgoe, and Todd, *J.*, 1946, 833; Howard, Kenner, Lythgoe, and Todd, *ibid.*, p. 861). The adaptation of this route to the synthesis of adenosine has been studied and had in fact been

successful before various difficulties encountered in the application of our general procedure to the same end have been surmounted. Since the result represents the first recorded synthesis of a naturally occurring purine nucleoside, it is desirable that it be recorded at this stage.

As originally described by Fischer and Helferich (*loc. cit.*) the method was not very attractive, but modifications recently introduced (Davoll, Lythgoe, and Todd, *loc. cit.*) have rendered the preparation of the necessary intermediate 2 : 8-dichloroadenine (I) comparatively simple and so removed one of its main drawbacks. Elsewhere we have described the preparation of acetobromo-D-ribofuranose, and have employed it to effect the first synthesis of the natural pyrimidine nucleoside, cytidine (Howard, Lythgoe, and Todd, *J.*, 1947, 1052). Although the configuration at C_1 in this compound has not been determined, the fact that it yielded cytidine (3-β-D-ribofuranosidocytosine) when condensed with 2 : 4-diethoxypyrimidine and the product treated with ammonia, and that it was also used to prepare 7-β-D-ribofuranosidotheophylline (Howard, Lythgoe, and Todd, *loc. cit.*), encouraged the belief that it, or the corresponding chloro-compound, would react with the silver salt of 2 : 8-dichloroadenine to yield a β-glycoside from which adenosine might be prepared. In view of the great ease with which acetobromoribofuranose loses hydrogen bromide, it was decided that the reaction would be better carried out with the corresponding acetochloro-sugar, which, if rather less reactive, is more stable and therefore more likely to give clean reaction products. 1 : 2 : 3 : 5-Tetra-acetyl-D-ribofuranose was treated with dry ethereal hydrogen chloride, and the crude syrupy acetochloro-D-ribofuranose at once refluxed in xylene solution with 2 : 8-dichloroadenine silver. Deacetylation of the product gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine* (II) in good yield; the stereochemical configuration of (II) was deduced from the fact that on titration with sodium metaperiodate it yielded the same fission product as 2 : 8-dichloro-9-β-D-glucopyranosidoadenine. Hydrogenation of (II) in aqueous sodium hydroxide in presence of a palladised barium sulphate catalyst replaced the halogen atoms by hydrogen and yielded 9-β-D-*ribofuranosidoadenine* (III), identical with a specimen of adenosine prepared from yeast ribonucleic acid by the method of Bredereck, Martini, and Richter (*Ber.*, 1941, **74**, 694). The identity of the two materials was established by m. p. and mixed m. p., optical rotation, periodate titration, and a comparison of *X*-ray powder photographs. Further confirmation was obtained by preparation of their picrates, which were identical in m. p. and mixed m. p.

The synthesis described provides final confirmation of the structure allotted to adenosine and to inosine (9-β-D-ribofuranosidohypoxanthine) which can be prepared from it by deamination. It is, of course, evident that an extension of the synthetic method along the lines used by Fischer and Helferich (*loc. cit.*) in their preparation of guanine glucoside should yield the natural nucleoside guanosine; experiments to this end will be reported upon later.



Experimental.

Acetochlororibofuranose.—1 : 2 : 3 : 5-Tetra-acetyl-D-ribofuranose (2·5 g.; Howard, Lythgoe, and Todd, *loc. cit.*) was dissolved in dry ethereal hydrogen chloride (50 c.c. saturated at 0°) and the solution set aside at 0° for 3 days. Solvent was removed under reduced pressure and the residue evaporated thrice with dry benzene from a bath at 15°. The product was a colourless syrup which was not further purified but was used immediately for the following experiment.

2 : 8-*Dichloro*-9-β-D-*ribofuranosidoadenine.*—The above crude acetochlororibose was dissolved in dry xylene (10 c.c.) and added to an azeotropically dried suspension of the silver salt of 2 : 8-dichloroadenine (3·5 g.) in xylene (80 c.c.). The mixture was refluxed during 5½ hours with exclusion of moisture, then filtered hot from silver chloride, and light petroleum (350 c.c. of b. p. 40—60°) added to the cooled filtrate. The powdery precipitate produced was collected, washed with light petroleum, then warmed with ethanol (35 c.c.) and allowed to cool. The triacetyl riboside was thus obtained as small buff-coloured crystals (1·82 g., 50%).

The triacetyl compound was dissolved in dry methanol (80 c.c.), cooled to 0°, methanolic ammonia (100 c.c. saturated at 0°) added, and the mixture set aside overnight at 0°. Evaporation of the solution followed by recrystallisation of the residue from water (charcoal) gave 2 : 8-*dichloro*-9-β-D-*ribofuranosidoadenine* (0·93 g.) as colourless needles, m. p. 232° (decomp.) (Found in material dried at 140°: C, 36·1; H, 3·6; N, 20·2. $C_{10}H_{11}O_4N_5Cl_2$ requires C, 35·8; H, 3·3; N, 20·8%).

Periodate Titrations.—(a) 2 : 8-*Dichloro*-9-β-D-*ribofuranosidoadenine.* Sodium metaperiodate (2 c.c. of 0·2663M) was added to a suspension of the glycoside (0·0743 g.) in water (total volume, 10 c.c.) and the

mixture allowed to stand at room temperature till solution was complete (20 hours). Titration of an aliquot portion with standard sodium arsenite showed that the periodate uptake corresponded to 1 mol./mol. of glycoside, and this uptake was unchanged after a further 24 hours. The solution obtained on periodate fission had $\alpha_D^{14°} + 0{\cdot}400°$ (l = 2 dm.), from which it can be deduced that the fission product had $[M]_D^{14°} + 9050°$.

(b) 2 : 8-*Dichloro*-9-β-D-*glucopyranosidoadenine*. The glycoside (0·0998 g.; Davoll, Lythgoe, and Todd, *loc. cit.*) was treated with sodium metaperiodate (5 c.c. of 0·2663M) in the same way as the above riboside. The final uptake of periodate after 42 hours was equivalent to 2·03 mols./mol. and the neutralised solution (2 c.c. of fission solution + 1·09 c.c. of N/20-sodium hydroxide) had $\alpha_D^{14°} + 0{\cdot}323°$ (l = 2 dm.), corresponding to $[M]_D^{14°} + 9160°$ for the fission product, in close agreement with the value obtained under (a) above.

9-β-D-*Ribofuranosidoadenine* (*Adenosine*).—2 : 8-Dichloro-9-β-D-ribofuranosidoadenine (0·6 g.) was dissolved in water (100 c.c.) and aqueous sodium hydroxide (4 c.c. of N), together with palladised barium sulphate (1 g. of material prepared from 22 g. barium sulphate and 1·8 g. palladous chloride). The mixture was shaken with hydrogen at room temperature for 7 hours; absorption of hydrogen had then ceased (total uptake 90 c.c.). After removal of catalyst by filtration the solution was exactly neutralised to phenolphthalein with hydrochloric acid (5·6 c.c. of 0·1N, corresponding to production of 3·44 millimoles of hydrogen chloride in the reduction; calc., 3·59 millimoles).

The neutralised filtrate was evaporated to dryness under reduced pressure and the residue dissolved in hot water (4 c.c.) and set aside. The crystalline product (0·32 g., 66%) was twice recrystallised from water, and then had m. p. 234—235°. In admixture with natural adenosine (m. p. 233—234°) the m. p. was 233—234° (Found in material dried at 110°: C, 45·2; H, 4·7; N, 26·6. $C_{10}H_{13}O_4N_5$ requires C, 45·0; H, 4·9; N, 26·2%).

The anhydrous synthetic product had $[\alpha]_D^{9°} - 58{\cdot}2°$ (c, 0·658 in water; l = 2 dm.), while the natural nucleoside had $[\alpha]_D^{11°} - 61{\cdot}7°$ (c, 0·706 in water; l = 2 dm.). On periodate titration the synthetic product (0·0263 g.) absorbed 1·1 mol. of oxidant/mol. giving a solution the optical rotation of which corresponded to $[M]_D^{9°} - 8700°$ for the fission product. Davoll, Lythgoe, and Todd (*loc. cit.*) have recorded $[M]_D^{19°} - 8560°$ for the periodate fission product of natural adenosine. The *X*-ray powder photographs of anhydrous natural and synthetic adenosine were examined in the Department of Crystallography in this University and found to be identical.

For further confirmation, the synthetic nucleoside was converted into the picrate which had m. p. 180—185° (decomp.) alone or mixed with authentic adenosine picrate [m. p. 180—185° (decomp.)] (Found in material dried at 110°: C, 38·5; H, 3·1; N, 23·0. Calc. for $C_{10}H_{13}O_4N_5,C_6H_3O_7N_3$: C, 38·7; H, 3·2; N, 22·6%).

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