656. *Deoxynucleosides and Related Compounds. Part IX.*[1] *A Synthesis of 3′-Deoxyadenosine.*

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3′-*O*-*p*-Nitrobenzenesulphonyladenosine reacts with sodium iodide in hot acetonylacetone to give a 3′-deoxy-3′-iodoadenosine that is converted by catalytic hydrogenation into 3′-deoxyadenosine. 2′-*O*-*p*-Nitrobenzenesulphonyladenosine does not appear to react with sodium iodide or lithium bromine save under conditions such that decomposition supervenes.

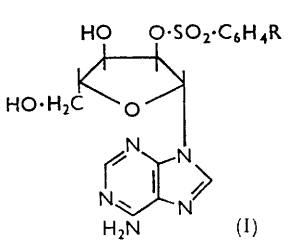
In earlier papers of this series,[1,2] syntheses of 2′-deoxyuridine and of thymidine were described in which the appropriate 2′-*O*-toluene-*p*-sulphonylribonucleosides were brought into reaction with sodium iodide and the resulting 2′-deoxy-2′-iodoribonucleosides subsequently reduced to the 2′-deoxyribonucleosides. The success achieved in these cases caused us to reconsider some earlier work along similar lines aimed at purine deoxynucleosides. Several years ago, Dr. A. M. Michelson in this laboratory attempted to prepare 2′-deoxyadenosine from 2′-*O*-methanesulphonyladenosine; treatment with lithium bromide under various conditions followed by reduction yielded no results, but direct reduction with lithium aluminium hydride or treatment with potassium thiocyanate followed by Raney nickel gave, in very small yield, products which could not be identified with certainty but seemed to be mixtures of at least two deoxynucleosides. Because of the very low yields, no further study of these products was made at that time. Undoubtedly the ease with which 2′-*O*-toluene-*p*-sulphonyluridine appears to react with sodium iodide is due to intermediate cyclonucleoside formation, but it seemed to us possible that, provided a more reactive sulphonyl group were employed, direct replacement by iodine could be achieved even in adenosine derivatives where there was little likelihood of cyclonucleoside formation.

Preliminary experiments were carried out on 2′-*O*-toluene-*p*-sulphonyladenosine (I; R = Me). This substance, originally synthesised from 3′,5′-di-*O*-acetyladenosine,[3] is more readily prepared by direct toluene-*p*-sulphonylation of 5′-*O*-acetyladenosine followed by deacetylation; the 2′-isomer can be separated readily from other products of the reaction by crystallisation. Sodium iodide did not react with 2′-*O*-toluene-*p*-sulphonyladenosine below temperatures (150—170°) at which much decomposition occurred. In the search for a derivative more susceptible to nucleophilic displacement, 5′-*O*-acetyladenosine was treated with *p*-nitrobenzenesulphonyl chloride in pyridine. From the deacetylated product two crystalline isomeric O-*p*-nitrobenzenesulphonyladenosines, m. p. 174° and 215° respectively, were isolated. The isomer of m. p. 174°, when heated with sodium iodide in acetonylacetone, gave a crystalline iodo-compound converted by catalytic hydrogenation into a deoxyadenosine. This synthetic material differed in m. p. from natural 2′-deoxyadenosine, but it could not be distinguished from the latter by paper chromatography and, like it, gave the cysteine–sulphuric acid reaction characteristic of deoxyglycosides.[4] As it failed to give any colour with the Dische reagent on paper, however, it was clearly not a 2′-deoxyglycoside [5] and, on acid hydrolysis, it yielded a sugar identified by paper chromatography as 3′-deoxyribose. It follows that the synthetic nucleoside is 3′-deoxyadenosine (III; R = H), and the iodo-compound from which it was derived is a 3′-deoxy-3′-iodoadenosine (III; R = I), presumably with the *xylo*-configuration. The original sulphonyl derivative of m. p. 174° we therefore formulate

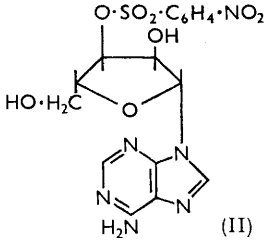
[1] Part VIII, Brown, Parihar, and Todd, *J.*, 1958, 4242.
[2] Brown, Parihar, Reese, and Todd, *Proc. Chem. Soc.*, 1957, 321; *J.*, 1958, 3035.
[3] Brown, Fasman, Magrath, and Todd, *J.*, 1954, 1448.
[4] Buchanan, *Nature*, 1951, **168**, 1091.
[5] Overend, Shafizadeh, and Stacey, *J.*, 1950, 1027.

as 3′-*O*-*p*-nitrobenzenesulphonyladenosine (II), and the isomer of m. p. 215° as 2′-*O*-*p*-nitrobenzenesulphonyladenosine (I; R = NO_2).

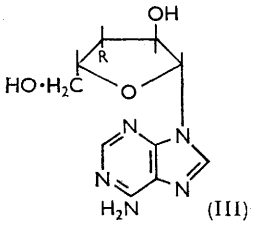
When the 2′-compound (I; R = NO_2) was heated for long periods with sodium iodide in acetonylacetone (at 125—145°) or with lithium bromide in dimethylformamide (at 95—135°), some reaction occurred, but it was accompanied by decomposition and no well-defined product could be isolated, nor could any deoxyglycoside be detected in the mixture after hydrogenation. The failure to obtain any 2′-deoxyadenosine in this way we attribute



(I)



(II)



(III)

mainly to steric hindrance, since inspection of models suggests that attack by large ions will be more hindered at $C_{(2')}$ than $C_{(3')}$; presumably decomposition supervenes under the conditions necessary to bring about reaction with bromide or iodide ions.

Experimental

Paper Chromatography.—Whatman No. 1 paper was used and R_F values quoted are for a descending butan-1-ol–acetic acid–water (4 : 1 : 5 v/v) system prepared by taking 50 c.c. of each phase equilibrated for 24 hr. together with 100 c.c. of fresh solvent.

2′-O-*Toluene*-p-*sulphonyladenosine.*—Toluene-*p*-sulphonyl chloride (3·5 g., 1 mol.) was added to a solution of 5′-*O*-acetyladenosine (5 g., 1 mol., dried at 110°) in dry pyridine (150 c.c.) at 0° and the mixture set aside at 0° for 48 hr. Water (25 c.c.) and saturated sodium hydrogen carbonate solution (200 c.c.) were added and the mixture was extracted with chloroform. The extract was thoroughly washed with sodium hydrogen carbonate solution, then with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was twice evaporated with a mixture of chloroform (20 c.c.) and toluene (5 c.c.), and the product finally left at 50°/0·1 mm. for 1 hr. The brownish resin (4·3 g.) so obtained was dissolved in methanol (80 c.c.), then cooled to 0°, and a saturated solution of ammonia in methanol (80 c.c.) was added. The solution was kept at 0° for 21 hr. and then evaporated under reduced pressure. Water was added to the residue, and the solution extracted with ethyl acetate. The dried extract ($MgSO_4$) was evaporated, the brown gum (3·4 g.) obtained dissolved in propan-2-ol, and benzene added until crystallisation began. The material which separated was fractionally crystallised from the same solvent mixture, giving pure 2′-*O*-toluene-*p*-sulphonyladenosine (0·8 g.), m. p. 224° undepressed by an authentic sample (m. p. 222—223°).

2′- *and* 3′-O-p-*Nitrobenzenesulphonyladenosine.*—*p*-Nitrobenzenesulphonyl chloride (1·65 g., 1·1 mol.) was added to 5′-*O*-acetyladenosine (2 g., 1 mol.; dried at 110°) in dry pyridine (60 c.c.) at 0°, and the mixture left at this temperature for 6 days, then at room temperature for a further 2 days. Water (10 c.c.) and saturated sodium hydrogen carbonate solution (50 c.c.) were added, the mixture was extracted with chloroform, and the extract was washed, dried, and evaporated. The residue was twice re-evaporated with ethanol (50 c.c.) and toluene (10 c.c.), then dissolved in methanol (40 c.c.). The solution was cooled to 0°, saturated methanolic ammonia (30 c.c.) was added, and the solution left at 0° for 7 hr. The solution was evaporated under reduced pressure and the residue extracted with hot benzene, the extract being discarded. The residue was fractionally recrystallised from propan-2-ol (in which the higher-melting isomer is very sparingly soluble when pure), giving 2′-O-p-*nitrobenzenesulphonyladenosine* (0·825 g.) as straw-coloured prisms, m. p. 215° (decomp.), R_F 0·91 (Found: C, 42·8; H, 4·0; N, 18·5. $C_{16}H_{16}O_8N_6S$ requires C, 42·5; H, 3·6; N, 18·6%), and 3′-O-p-*nitrobenzenesulphonyladenosine* (0·4 g.) as small, buff needles, m. p. 174° (decomp.), R_F 0·91 (Found: C,

42·7; H, 3·9; N, 18·8%). The infrared spectra (in Nujol) of both compounds showed bands at 1368—1372 and 1186—1188 cm.$^{-1}$ (·O·SO_2·), and at 1533—1538 and 1344—1350 cm.$^{-1}$ (NO_2).

3′-*Deoxy*-3′-*iodoadenosine*.—A solution of 3′-*O*-*p*-nitrobenzenesulphonyladenosine (214 mg.) and anhydrous sodium iodide (145 mg.) in acetonylacetone (4 c.c.) was heated at 115° (bath-temp.) for 5 hr. The cooled solution was filtered from sodium *p*-nitrobenzenesulphonate (87 mg., 87%), the latter being washed with a mixture of acetonylacetone and ether. The combined filtrate and washings were evaporated, acetonylacetone being removed at 50°/0·5 mm. The residue was subjected to countercurrent distribution in an automatic machine (ethyl acetate–water; 20·5 c.c. phases; 92 transfers). Tubes 34—70 were combined and evaporated. The residue was recrystallised from water, giving 3′-*deoxy*-3′-*iodoadenosine* (31 mg.) as colourless spherical crystalline aggregates, m. p. 186—188° (decomp.), R_F 0·84 (Found, in material dried at 110°/0·5 mm. for 1 hr.: C, 31·6; H, 3·6; N, 17·9. $C_{10}H_{12}O_3N_5I,\frac{1}{2}H_2O$ requires C, 31·2; H, 3·4; N, 18·1%).

3′-*Deoxyadenosine*.—A solution of the above iodo-compound (74 mg.) and sodium acetate (20 mg.) in water (25 c.c.) was shaken with 10% palladised charcoal (15 mg.) in hydrogen at room temperature and atmospheric pressure till no more hydrogen was absorbed. Catalyst was filtered off, the solution concentrated to small bulk, and ethanol added. The crystalline product which separated was recrystallised from propan-2-ol, giving 3′-*deoxyadenosine* as feathery needles, m. p. 212°, R_F 0·71 (Found, in material dried for 1 hr. at 110°/0·5 mm.: C, 47·8; H, 5·4; N, 27·9. $C_{10}H_{13}O_3N_5$ requires C, 47·8; H, 5·2; N, 27·9%), $\lambda_{max.}$ 259 mμ (ε 15,100), $\lambda_{min.}$ 227 mμ (ε 2400).

The synthetic nucleoside (4 mg.) was hydrolysed on the steam-bath for 1 hr. by 0·1N-hydrochloric acid (10 c.c.). The results of paper-chromatographic comparison of the sugar produced with other deoxypentoses are tabulated.

	R_F	Spray 1	Spray 2	Spray 3
Hydrolysis product ...	0·50	—	Pink+	Purple-brown+++
3-Deoxyribose	0·50	—	Pink+	Purple-brown+++
3-Deoxyarabinose	0·43	—	Pink++	Purple-brown++
2-Deoxyribose	0·41	Purple+++	Pink-brown+++	Brown+

Spray reagents: (1) Dische reagent,[6] (2) cysteine–sulphuric acid,[4] (3) aniline phthalate.[7]

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[6] Buchanan, Dekker, and Long, *J.*, 1950, 3162.
[7] Partridge, *Nature*, 1949, **164**, 443.